Multiple Endocrine Neoplasia Syndromes from Genetic and Epigenetic Perspectives

Biomarker Insights
Volume 13: 1–9

DOI: 10.1177/1177271918785129

Fatemeh Khatami[1] and Seyed Mohammad Tavangar[1,2]

[1]Chronic Diseases Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran. [2]Department of Pathology, Doctor Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

ABSTRACT: Multiple endocrine neoplasia (MEN) syndromes are infrequent inherited disorders in which more than one endocrine glands develop noncancerous (benign) or cancerous (malignant) tumors or grow excessively without forming tumors. There are 3 famous and well-known forms of MEN syndromes (MEN 1, MEN 2A, and MEN 2B) and a newly documented one (MEN4). These syndromes are infrequent and occurred in all ages and both men and women. Usually, germ line mutations that can be resulted in neoplastic transformation of anterior pituitary, parathyroid glands, and pancreatic islets in addition to gastrointestinal tract can be an indicator for MEN1. The medullary thyroid cancer (MTC) in association with pheochromocytoma and/or multiple lesions of parathyroid glands with hyperparathyroidism can be pointer of MEN2 which can be subgrouped into the MEN 2A, MEN 2B, and familial MTC syndromes. There are no distinct biochemical markers that allow identification of familial versus nonfamilial forms of the tumors, but familial MTC usually happens at a younger age than sporadic MTC. The *MEN1* gene (menin protein) is in charge of MEN 1 disease, CDNK1B for MEN 4, and RET proto-oncogene for MEN 2. The focus over the molecular targets can bring some hope for both diagnosis and management of MEN syndromes. In the current review, we look at this disease and responsible genes and their cell signaling pathway involved.

KEYWORDS: Multiple endocrine neoplasia (MEN), genetic, epigenetic, methylation, oncogenes

RECEIVED: January 25, 2018. **ACCEPTED:** May 24, 2018.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Seyed Mohammad Tavangar, Department of Pathology, Doctor Shariati Hospital, Tehran University of Medical Sciences, Jalale Ale Ahmad Ave., Tehran, Iran. Email: Tavangar@ams.ac.ir

Introduction

Multiple endocrine neoplasia (MEN) disorders are infrequent and hereditary diseases that can be developed into the number of endocrine glands and result in tumor formation or grow exceptionally no tumor creation.[1–4] The MENs are run in families because they are the exact consequence of genetic mutations and their symptoms are completely dissimilar dependent on the involving glands.[5–7] The profiling and screening of candidate genes can be informative to detect disease people who have or are susceptible to MEN syndromes.[8–12] The MEN syndromes occur in 3 forms which are types 1, 2A, and 2B and through specific novel variants such as MEN 4.[13] These main types have some similarity and are atypically outsized glands with additional hormone production.[14] The genetic alterations (mutation) are mainly responsible for MEN syndrome formation and the main candidate gene accountable for type 1 disease is well known, whereas in people with types 2A and 2B, defects in some genes can be responsible for these 2 types of disease formation. People with MEN type 1 usually develop tumors of 2 or more often in the parathyroid gland, pancreas, pituitary gland, and less often in thyroid gland and adrenal glands.[15–18] More often than not, people with MEN type 1 will develop the parathyroid-related benign tumors with excessive parathyroid hormone production.[19] This extra parathyroid hormone generally increases the calcium levels in the blood or even occasionally triggering formation of kidney stones. In 30% to 80% of people with MEN 1 hormone-producing cells (islet cells) of the pancreas, tumors can be seen (Table 1).

MEN Type 1

Multiple endocrine neoplasia 1 (MEN 1, OMIM no. 131100), famous as Wermer disease, is a familial disease and autosomal dominant cancer connected with the endocrine (hormone-producing) glands neoplasia.[20–22] The maximum joint tumors with MEN1 are the parathyroid glands, islet cells of the pancreas, and pituitary glands.[13,23] Additional rare endocrine tumors realized in MEN1 contain adrenal cortical tumors, carcinoid tumors and infrequent pheochromocytomas, and some parts of the digestive tract. Moreover, there are some nonendocrine tumors in MEN1 such as facial angiofibromas, collagenomas (flesh-colored tumors on the skin), lipomas, leiomyomas, meningiomas, and ependymomas.[13]

Men1 is the most often happening form of MENs and it is more often than not associated with primary hyperparathyroidism (distinguished by the presence of parathyroid adenomas or hyperplasia), which happens in about 90% of patients.[24] The treatment strategy typically can be surgery and drug that increases dopamine activity prescription, an effective prolactin-inhibiting factor in patients with prolactin-secreting pituitary tumors.[25] Moreover, surgery or a proton pump inhibitor (a drug that blocks gastric acid secretion) could be used for patients with gastrinomas to reduce levels of gastric acid and peptic ulcers. There are some suggestions over the comparison of the conservational management and surgery. For example, MEN1 patient's nonfunctioning pancreatic neuroendocrine tumors with size more than 2 cm would be preferred to manage through observant waiting, while the surgery in nonfunctioning

Table 1. The major conditions and features of MEN (multiple endocrine neoplasia).

MEN TYPE	GENE	CONDITIONS (FEATURES)
MEN 1 (Wermer)	*MEN 1* (menin)	Hyperparathyroidism (95%) Pancreas tumors (30%-80%) Pituitary gland tumors (30%-42%) Rarely (facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas)
MEN2A (Sipple)	*RET* (specially codon 634)	Thyroid gland tumors (specifically medullary carcinoma) (95%) Pheochromocytoma (tumor of the adrenal glands) (40%-50%) Hyperparathyroidism (10%-20%)
MEN2b (multiple mucosal neuroma syndrome)	*RET* (specially codon 918)	Neuromas (99%) Physical characteristics similar to those in people with Marfan syndrome (99%) Thyroid gland tumors (specifically medullary carcinoma) (95%)
MEN4	*CDNK1B*	Parathyroid and anterior pituitary tumors (possibly associated with adrenal, renal, and reproductive organ tumors)

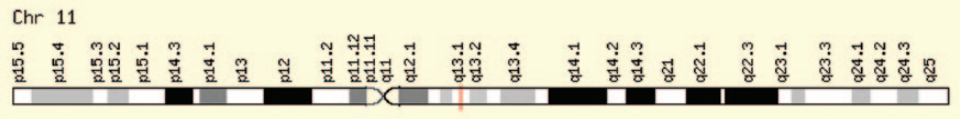

Figure 1. *MEN1* gene in genomic location: bands according to ensemble (http://www.genecards.org/cgi-bin/carddisp.pl?gene=MEN1).

pancreatic neuroendocrine tumors with size more than 3 cm should be taken into consideration.[26,27]

MEN1 disease is a consequence of the *MEN1* gene mutation whose genetic locus is chromosome 11q13 (Figure 1).[28,29] The role of *MEN1* gene is a tumor suppressor confirmed by microsatellite analysis in cancerous tissues of MEN1 patients.[30–33]

Germ line mutation in the *MEN1* gene resulting in loss of heterozygosity (*LOH*) at both alleles of MEN1 in the endocrine tumor and can be extent throughout the coding region of the gene.[34,35] The protein product of *MEN1* comprises 610 residues and is completely consensus from *Drosophila melanogaster* to humans,[36] contrary to yeast or *Caenorhabditis elegans*, signifying its new evolutionarily origin.[36] Despite the fact that during mouse embryogenesis, *MEN1* gene is ubiquitously expressed in countless tissues and organs during mouse embryonic development,[37–39] its role is completely restricted and tissue specific in the way that even exhibiting contrasting function between different organs.[38] In endocrine organs, *MEN1* suppresses tumorigenesis in some organs, such as lung, prostate, and breast, and it makes worse diabetes in mouse models.[40–46] Interestingly, there are some reports over the role of *MEN1* function of further organs such as liver and bone.[47–50] In mouse mesenchymal and osteoblastic cells, it is related to β-catenin, cell-cell adhesion, and gene transcription factor, which is essential for osteoblast differentiation.[49] Also, MEN1 protein (menin) is considered to maintain bone morphogenetic protein 2 (BMP-2), TGF-β super family of proteins, and Runt-related transcription factor 2 (Runx2), resulting in mesenchymal cells to osteoblasts differentiation.[51] Overexpression of MEN1 repressed the ALP activity induced by *JunD*. Actually, it has been recommended that menin destroys the maturation of osteoblast, through stopping the differentiation of *JunD*.[52,53] Menin can be activated in fibrinogenes via TGF-beta.[54] It has been shown that menin inhibits gene transcription through different chromatin-modifying enzymes or posttranscriptionally acting. What is more is G2-M phase transition stopping through *cyclin B2* expression.[55,56] It also plays its role through JunD-mediated gene transcription and other mechanisms.[55,57-60] More than that menin in a straight line interacts with the p65 subunit of *NF-κB* to repress *NF-κB*–dependent transcription.[61,62] There are some suggesting interactions with the *PTN* gene as a pro-proliferative receptor in lung cancer cells for the inhibition of complex 2 (*PRC2*) attachment to the PTN gene promoter in addition to enhancing the suppressive chromatin spot *H3K27me3*.[41]

Menin is able to induce posttranscriptional modification through increasing the microRNA expression like microRNA-26a (*miR-26a*) which is crucial for osteoblastic differentiation.[63] More than nuclear localization of menin, it is present in cytoplasm or even extracellular spaces suggesting that it has additional role in control of multiple signaling pathways, ranging from *Ras* to *Akt* to Hedgehog signaling (Figure 2). It was shown that with supporting of the transforming growth factor type β signaling pathway, cell proliferation inhibition removed.[65] For *Wnt* signaling and glyco-kipoprotein emission the trascriptional co-activator btea-caten controls homeostasis in embryonic and adult development.[66] Menin holds back extracellular regulated protein kinase-1/2 (*ERK-1/2*) mitogen-activated protein kinase pathway which is a downstream target in *Ras* pathway.[67–69] The correlation of menin with reduced activity of protein kinase *Akt1* in cultured cells and mouse pancreatic denoted that translocation of *Akt1* to the cell membrane is inhibited by menin.[70] Further studies had shown that the transcription factor *FOXO1* in the cytoplasm of hepatocytes

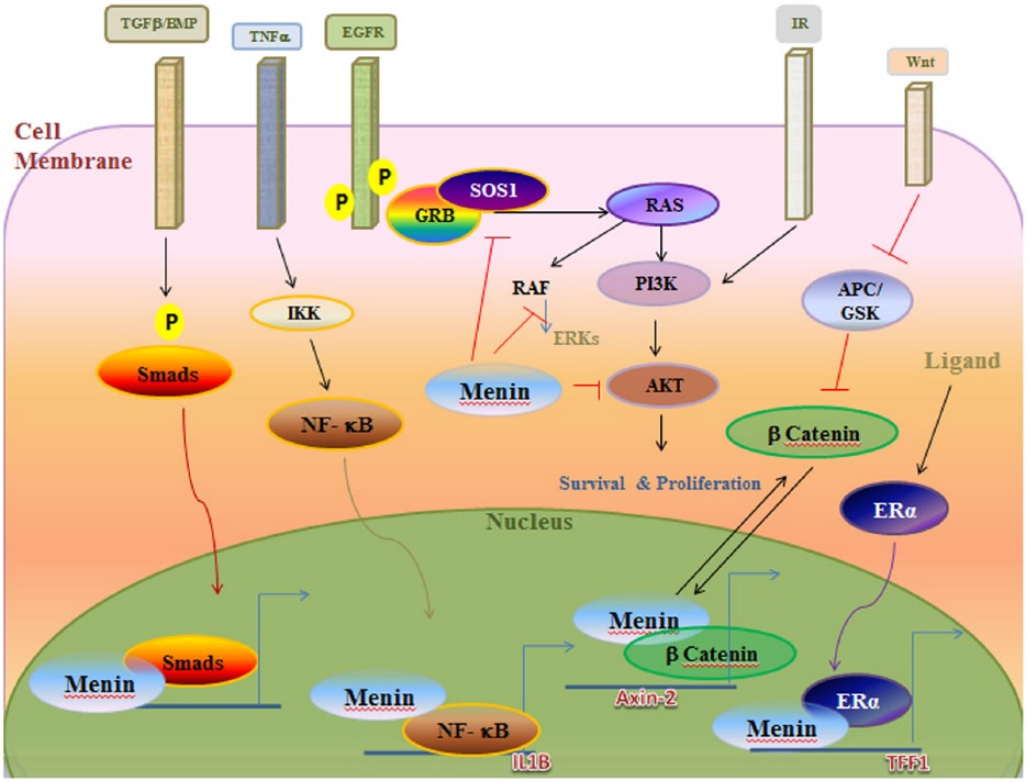

Figure 2. Menin in numerous cell signaling pathways.[64]

correlated with menin; however, it is uncertain how menin cooperates with *FOXO1* and what are its biological outcomes.[71] There are some indicators of menin role in taking on *PRMT5* to the promoter of the *Gas1* gene, a fundamental part for binding of Sonic hedgehog (*Shh*) ligand, to activate the Hedgehog signaling pathway.[62]

It can be said that menin mediated inhibition of cell proliferation inhibition through interaction with (a) histone-modifying enzymes (*MLL*, *EZH2*, and *HDACs*); (b) the relations with several transcription factors, such as *JunD*, nuclear factor κB (*NF-κB*), peroxisome proliferator-activated receptors (*PPARγ*), and vitamin D receptor (*VDR*), to stimulate or repress gene transcription; (c) cell proliferation arresting by means of transforming growth factor β_1 (*TGF-β*) signaling and *Wnt/β-catenin* pathways; (d) the destruction of pro-proliferative factors such as insulinlike growth factors I and II (Igf-I and Igf-II) and parathyroid hormone-related protein (PTHrP) involved in endocrine tumors; and (e) the direct effect on cell cycle progression.[13,57,72]

More often than not, in 5% to 10% of MEN1 patients, no mutations of the *MEN1* gene can be detected that could harbor mutations involving other genes[34,73] such as the *CDNK1B* gene (12p13.1-p12) responsible for coding 196 amino acid cyclin-dependent kinase inhibitor (*CK1*) *p27kip1* mutation, highlighting as a responsible gene of recessive MEN-like syndrome referred to as MEN4.[74] The exact MEN4 tumorigenesis molecular mechanisms are not clear yet, although it is supposed that the mutated allele possibly will be responsible for the reduction of p27 protein localized in the nucleus and, thus, competent to exert its role of negative regulator of cell cycle progression and cell growth. Now, 9 dissimilar *CDKN1B* pathogenic modifications have been recognized but no precise medical features is available to discriminate MEN4 from MEN1.

In addition to genetic alterations, there are some epigenetic mechanisms that act as a regulatory element through changing the gene expression patterns without altering the sequence of the genome.[75] Between epigenetic mechanisms and DNA methylation, the important ones that happen in around 3% of cytosines of cytosine-guanine dinucleotide (CpG) islands are present in the genome.[76] Menin can interact with lysine methyltransferase 2D (*MLL2*) and regulate its histone methyl transferase activity.[77] It was shown that insulinlike growth factor 2 (*Igf2*) was overexpressed in *Men1* mutant mice as a result of hypermethylation of the intragenic differentially methylated regulatory regions (DMR2) of the *Igf2* gene.[78] Promoter hypermethylation was shown in one of the cell cycle regulator genes (*RB1*, *P14ARF*, *P15 (INK4b)* (*CDKN2B*), *P16* (*CDKN2A*), *P21* (*CDKN1A*), *P27*, and *P73*(*TP73*)) in pituitary tumors, that is, one of the MEN1-associated tumors.[79] Moreover, there are some evidence of promoter hypermethylation in the *retinoblastoma 1, P14 (ARF), P16, P73*, metalloproteinase inhibitor 3 (*TIMP3*), *O*-6-methylguanine DNA methyltransferase (*MGMT*), *DAPK* (*DAPK1*), *THBS1*, and *CASP8* genes.[80–83] Also, the fibroblast growth factor receptor (*FGFR2*), a member of the FGF family with a critical role in

pituitary development, decreased in human pituitary tumors as a result of gene promoter methylation. The genotype/phenotype association in Korean MEN1 patients suggested some altered DNA methylations to track the main reason of tumorigenesis.[84]

MEN Type 2

Multiple endocrine neoplasia type 2 (MEN2) is a hereditary disease resulting in additional abnormal activation of one or more of the endocrine glands which could be resulting in a wide range of tumor formations, including adrenal (about half the time), parathyroid (20% of the time), and thyroid (almost all of the time).[85] MEN2 is triggered by malfunction of the *RET* (REarranged during Transfection) gene.[86,87] MEN 2 is classified to 3 different subtypes: MEN 2A, MEN 2B, and FMTC (familial medullary thyroid carcinoma) with the possibility of medullary carcinoma of the thyroid (MTC) development. In fact, both MEN 2A and MEN 2B have a bigger hazard for pheochromocytoma, whereas MEN 2A has a higher possibility for parathyroid adenoma or hyperplasia.[88] MTC classically happens in early childhood in MEN 2B, first years of adulthood in MEN 2A, and middle age in FMTC.[89,90] Although MEN 2 was detected the first time at the University Hospital of Freiburg, Germany, in the 19th century, the connection of an MTC and a pheochromocytoma was initially explained in 1961.[91–93] Between different MEN 2 subtypes, MEN 2A is the mainly frequent form which develops MTC in the form of multifocal, bilateral, and nearly linked to the C-cell hyperplasia.[13,94,95] Half of MEN 2A patients are at the risk of pheochromocytoma involving both adrenal glands[96–98] and one-fourth of MEN 2A patients are able to grow multiple adenomatous parathyroid glands with hyperparathyroidism.[99] Moreover, co-occurrence of Hirschsprung's disease (HSCR) and coetaneous lichen amyloidosis was shown.[100–102] MEN 2 is the source of numerous tumors in one patient, although not essentially at the equal time.[87]

Indicators of MEN2 can be a lump in the front of the neck and sweating, irregular heartbeat, and headaches.[103] MEN2 can be identified with several blood and urine tests, a biopsy or computed tomographic scan, magnetic resonance imaging, or ultrasound scans. The adrenal tumors are identified pheochromocytoma, and the thyroid tumors are described as medullary thyroid carcinoma (MTC) which inherited in dominant autosomal pattern.[22,104-108] In fact, parafollicular C cells of the thyroid gland and calcitonin-secreting cells can give rise to MTC which is approximately the first appearance of MEN2 all times in very young children.[109] It can be led to hyperplasia of the C cells and make the patients candidate for total thyroidectomy (TT), whereas patients with hyperplasia progressed to carcinoma are not treatable through this operation.[110] In addition, genetic testing is another accessible tool, so checking the mutation of some candidate genes involving *RET* exons 10, 11, 13, 14, 15, and 16 can be informative to determine that many MEN2 carriers undergo TT ahead of showing MTC symptoms.[22] The MTCs are likely to metastasize to central and lateral, cervical, and adjacent lymph nodes or farther in lung, liver, or bone.[22] The aggressiveness of MTC linked to the MEN2 is dependent to the exact mutated *RET* codon (Table 2),[112,113] so finding the genotype-phenotype correlation has been specified recently.[114,115]

RET proto-oncogene chromosomal locus is 10q11.21 and encodes a transmembrane receptor and member of the tyrosine protein kinase family protein with 1114 amino acids and 124 319 Da weight (Figures 3 and 4).

The *Ret* gene established is expressed in definite line of cells which are originated from neural crest-like C cells of thyroid glands, migratory neural crest cells, the cells of dorsal-ventral axis of the neural tube, autonomic ganglion cells, and cells of enteric nervous system.[119–121]

The expression of *RET* gene stays controlled through DNA-binding factors to adjust transcription-like growth response protein-1 (*EGR-1*), transcription factor *Spi-1/PU*, and *Sp3* transcription factor more than enhancer elements.[122–125] The alternative splicing of 3' exonic regions of *RET* transcript is leading to 3 protein isoforms: *RET9, RET43*, and *RET51* with different carboxyl terminus.[126–128] *RET* includes a big extracellular domain, same as other receptor tyrosine kinases that are another cell surface receptors and reveals multiple cadherin-like domains more than calcium-binding site.[129] This extracellular region is made of 4 cadherin-like repeats, important for stabilizing *RET* dimers, plus a membrane-proximal cysteine-rich module, in support of protein conformation and ligand binding.[129–132] After translation of *RET* transcripts, protein undergoes glycosylation as a post-translational modification and an immature 155 KDa is produced which is additional processed and a mature plasma membrane is formed.[133,134] *RET* is involving in different cell signaling pathways and its role is completed through attachment of proteins of the glial cell line–derived neurotrophic factor (*GDNF*) family ligands (*GFLs*).[135] However, this attachment is mediated through an additional coreceptor: which is one of the 4 *GDNF* family receptor-α (*GFR*α) family members.[136] An additional new cell surface protein called Ret ligand 2 (*RETL2*) acts as a go-between *GDNF*-dependent ret signaling.[136] The extracellular domain of the *RET* has a kind of mutation which results in nonsynonymous substitution of amino acids (missense mutation), and this mutation frequently occurred in exons 10 and 11 and very uncommon mutations in exons 13, 14, and 15 which change cysteine codons.[136,137] The *RET* dimerization to form the active protein is influenced by replacing cysteine amino acids by other amino acid residues resulting in oncogenic potency of these *RET* mutations.[138] In MEN 2A, mainly *RET* mutations of codon 634 resulting to replace Cys634 by arginine (*RET* Cys634Arg) leads to parathyroid disease.[139] It has been shown that this RET mutation also could be presented in Hirschsprung's disease connected to

Table 2. Risk for aggressive MTC based on genotype and recommended interventions.

ATA[A] RISK LEVEL	LEVEL D (HIGHEST RISK)	LEVEL C	LEVEL B	LEVEL A
Pathogenic variants[b,c]	p.Ala883Phe p.Met918Thr p.Val804Met+p.Glu805Lys[d] p.Val804Met+p.Tyr806Cys[d] p.Val804Met+p.Ser904Cys[d]	p.Cys634Arg/Gly/Phe/Ser/Trp/Tyr	p.Cys609Phe/Arg/Gly/Ser/Tyr p.Cys611Arg/Gly/Phe/Ser/Trp/Tyr p.Cys618Arg/Gly/Phe/Ser/Tyr p.Cys620Arg/Gly/Phe/Ser/Trp/Tyr p.Cys630Arg/Phe/Ser/Tyr p.Asp631Tyr p.633/9 bp dup p.634/12 bp dup p.Val804Met+p.Val778Ile[d]	p.Arg321Gly p.531/9 bp dup p.532 dup p.Cys515Ser p.Gly533Cys p.Arg600Gln p.Lys603Glu p.Tyr606Cys p.635/insert ELCR; p.Thr636Pro p.Lys666Glu p.Glu768Asp p.Asn777Ser p.Leu790Phe p.Val804Leu/Met p.Gly819Lys p.Arg833Cys p.Arg844Gln p.Arg866Trp p.Ser891Ala p.Arg912Pro
Age of prophylactic surgery	As soon as possible in first year of life	<5 y	Consider <5 y; may delay if criteria met[e]	May delay beyond age 5 y if criteria met[e]

Adapted from American Thyroid Association Guidelines Task Force (2009).[111]
[a]ATA, American Thyroid Association.
[b]p.Ser649Leu and p.Tyr791Phe have been removed from this list as they were reclassified as benign variants.[116]
[c]Pathogenic variant designations have not been edited by *Gene Reviews* staff and may not be standard nomenclature.
[d]Pathogenic variants in *cis* configuration on one allele.
[e]Criteria: typical annual basal and or stimulated serum calcitonin; normal yearly neck ultrasound examination; family history of fewer aggressive MTC.

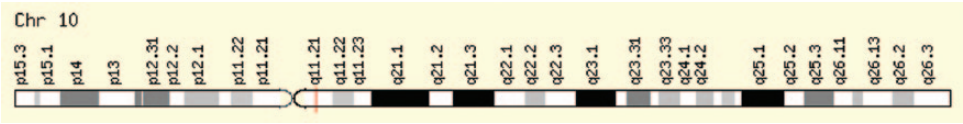

Figure 3. *RET* gene in genomic location: bands according to Ensembl, locations according to GeneLoc (and/or Entrez Gene and/or Ensembl if different) taken from http://www.genecards.org/cgi-bin/carddisp.pl?gene=RET.

the MEN 2A,[140] and renal malformations in RET^{MEN2b} transgenic mice linked to MEN 2A activating mutations.[141] The behavior of *RET Cys634Arg* mutation presents an extra aggressive MEN2A phenotype than Cys634Tyr mutation.[142] Opposite to some mutations of FMTC and MEN 2A, MEN 2B patients have mutation of codon 918 in exon 16 during which threonine (ACG) amino acid takes the place of methionine (ATG).[90,143] Despite the fact that *RET* hotspots are known, some recent studies have suggested that the whole coding region of the *RET* gene is supposed to be sequenced because a comprehensive analysis of the *RET* gene can reveal multiple germ line mutations in MEN 2.[144,145] The individualized prophylactic TT for MEN 2–related MTC was suggested according to prognostic incorporated testing of *RET* mutations and pre-serum calcitonin (Ct) levels in a group of Chinese.[146]

In addition to genetic mutations related to RET, there are some epigenetic profiles such as hypermethylation of CpG island promoters which is associated with transcriptional inactivation of tumor suppressor genes in different tumor formations.[147] For example, combined methylation of *RASSF1A* and *p16* was established in MEN2-related pheochromocytomas.[148] In fact, inactivation of *RASSF1A* (RASSF1) through promoter hypermethylation can happen in thyroid cancer development and *RASSF1* is tumor suppressor that is critical for phosphatidylinositol 3-kinase (*PI3K*)/*Akt*[88] pathway.[149–151]

Conclusions

MEN syndromes are a collection of autosomal dominant disease including MEN 1 (Wermer syndrome), MEN 2 (multiple endocrine adenomatosis), MEN 2A (Sipple syndrome), MEN 2B (mucosal neuroma syndrome), and MEN4. The information of MEN's genetic alterations and the connection among genotype and phenotype could be beneficial for MEN disease management. The most important responsible genetic mutations are *MEN1* gene in *MEN1* (menin), *RET* gene mutation codon 634 in MEN2A, and *RET* gene mutation codon 918 in MEN2B, and *CDNK1B* in MEN4.

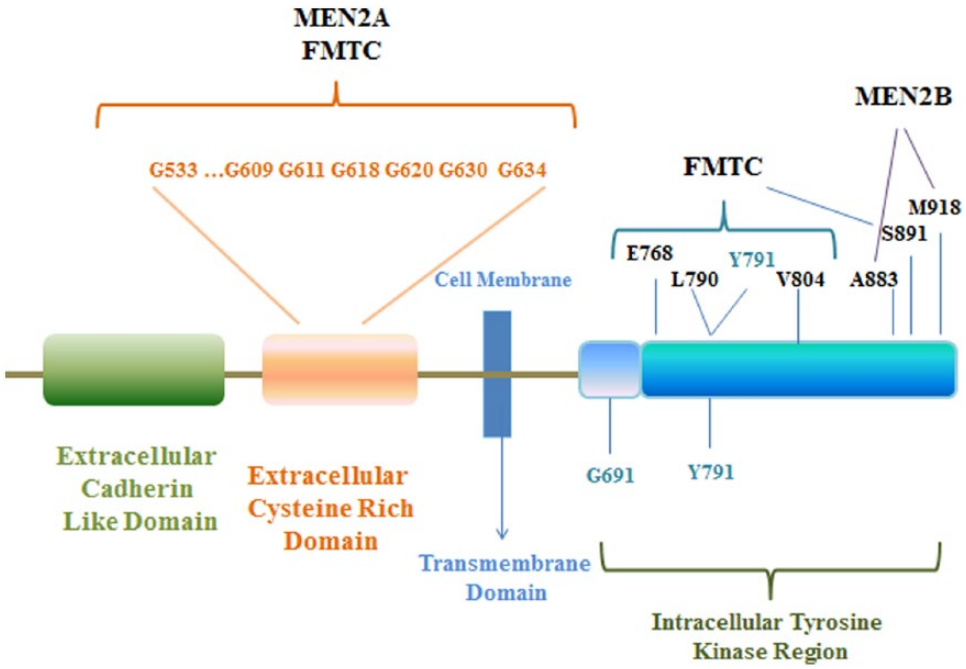

Figure 4. Activating mutations in multiple endocrine neoplasia over the RET proto-oncogene.[117,118]

Acknowledgements

The authors specially thank Endocrinology and Metabolism Population Sciences Institute.

Author Contributions

SMT conceived of the presented idea and developed the theory. FK wrote the manuscript and developed it to the final version.

REFERENCES

1. Haghpanah V, Soliemanpour B, Heshmat R, et al. Endocrine cancer in Iran: based on cancer registry system. *Indian J Cancer*. 2006;43:80–85.
2. Calender A. Multiple endocrine neoplasia: genetic aspects. *Bull Acad Natl Med*. 2010;194:81–95; discussion 95-96.
3. Larijani B, Shirzad M, Mohagheghi M, et al. Epidemiologic analysis of the Tehran Cancer Institute Data System Registry (TCIDSR). *Asian Pac J Cancer Prev*. 2004;5:36–39.
4. Larijani B, Mohagheghi MA, Bastanhagh MH, et al. Primary thyroid malignancies in Tehran, Iran. *Med Princ Pract*. 2005;14:396–400.
5. Carney JA. Familial multiple endocrine neoplasia: the first 100 years. *Am J Surg Pathol*. 2005;29:254–274.
6. Carney JA. Familial multiple endocrine neoplasia syndromes: components, classification, and nomenclature. *J Intern Med*. 1998;243:425–432.
7. Callender GG, Rich TA, Perrier ND. Multiple endocrine neoplasia syndromes. *Surg Clin N Am*. 2008;88:863–895.
8. Falchetti A. Genetic screening for multiple endocrine neoplasia syndrome type 1 (MEN-1): when and how. *F1000 Med Rep*. 2010;2:14.
9. Calender A. Genetic testing in multiple endocrine neoplasia and related syndromes. *Forum (Genova)*. 1998;8:146–152.
10. Thakker RV. Multiple endocrine neoplasia. *Horm Res Paediatr*. 2001;56:72.
11. O'Riordain DS, O'Brien T, Grant CS, Weaver A, Gharib H, van Heerden JA. Surgical management of primary hyperparathyroidism in multiple endocrine neoplasia types 1 and 2. *Surgery*. 1993;114:1031–1039.
12. Haghpanah V, Shooshtarizadeh P, Heshmat R, Larijani B, Tavangar SM. Immunohistochemical analysis of survivin expression in thyroid follicular adenoma and carcinoma. *Appl Immunohistochem Mol Morphol*. 2006;14:422–425.
13. Romei C, Pardi E, Cetani F, Elisei R. Genetic and clinical features of multiple endocrine neoplasia types 1 and 2. *J Oncol*. 2012;2012:705036.
14. Marx SJ. Molecular genetics of multiple endocrine neoplasia types 1 and 2. *Nat Rev Cancer*. 2005;5:367–375.
15. Marx S, Spiegel AM, Skarulis MC, Doppman JL, Collins FS, Liotta LA. Multiple endocrine neoplasia type 1: clinical and genetic topics. *Ann Intern Med*. 1998;129:484–494.
16. Mahta A, Haghpanah V, Lashkari A, Heshmat R, Larijani B, Tavangar SM. Non-functioning pituitary adenoma: immunohistochemical analysis of 85 cases. *Folia Neuropathol*. 2007;45:72–77.
17. Shirzad M, Larijani B, Hedayat A, et al. Diagnostic value of frozen section examination in thyroid nodule-surgery at the Shariati Hospital (1997-2000). *Endocr Pathol*. 2003;14:263–268.
18. Nasseri Moghaddam S, Malekzadeh R, Sotoudeh M, et al. Lower esophagus in dyspeptic Iranian patients: a prospective study. *J Gastroenterol Hepatol*. 2003;18:315–321.
19. Marx S, Agarwal S, Kester M, et al. Multiple endocrine neoplasia type 1: clinical and genetic features of the hereditary endocrine neoplasias. *Recent Prog Horm Res*. 1999;54:397–438; discussion 438–439.
20. Busygina V, Bale AE. Multiple endocrine neoplasia type 1 (MEN1) as a cancer predisposition syndrome: clues into the mechanisms of MEN1-related carcinogenesis. *Yale J Biol Med*. 2006;79:105–114.
21. Jeong YJ, Oh HK, Bong JG. Multiple endocrine neoplasia type 1 associated with breast cancer: a case report and review of the literature. *Oncol Lett*. 2014;8:230–234.
22. Brandi ML, Gagel RF, Angeli A, et al. Consensus: guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab*. 2001;86:5658–5671.
23. Lemmens I, Van de Ven WJ, Kas K, et al. Identification of the multiple endocrine neoplasia type 1 (MEN1) gene. *Hum Mol Genet*. 1997;6:1177–1183.
24. Anlauf M, Perren A, Meyer CL, et al. Precursor lesions in patients with multiple endocrine neoplasia type 1-associated duodenal gastrinomas. *Gastroenterology*. 2005;128:1187–1198.
25. Molitch ME. Disorders of prolactin secretion. *Endocrinol Metab Clin North Am*. 2001;30:585–610.
26. Nell S, Verkooijen HM, Pieterman CR, et al. Management of MEN1 related nonfunctioning pancreatic NETs: a shifting paradigm: results from the Dutch-MEN1 Study Group. *Ann Surg*. 2018;267:1155–1160.
27. Triponez F, Sadowski Veuthey MSD, Pattou F, et al. Long-term follow-up of MEN1 patients who do not have initial surgery for small ≤2 cm nonfunctioning pancreatic neuroendocrine tumors, an AFCE and GTE Study: Association Francophone de Chirurgie Endocrinienne & Groupe d'Etude des Tumeurs Endocrines. *Ann Surg*. 2017;268:158–164.
28. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science*. 1997;276:404–407.
29. Byström C, Larsson C, Blomberg C, et al. Localization of the MEN1 gene to a small region within chromosome 11q13 by deletion mapping in tumors. *Proc Natl Acad Sci U S A*. 1990;87:1968–1972.

30. Larsson C, Skogseid B, Öberg K, Nakamura Y, Nordenskjöld M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. *Nature*. 1988;332:85–87.
31. Thakker RV, Bouloux P, Wooding C, et al. Association of parathyroid tumors in multiple endocrine neoplasia type 1 with loss of alleles on chromosome 11. *N Engl J Med*. 1989;321:218–224.
32. Farnebo F, Teh BT, Kytöla¨S, et al. Alterations of the MEN1 gene in sporadic parathyroid tumors. *J Clin Endocrinol Metab*. 1998;83:2627–2630.
33. Tavangar SM, Larijani B, Mahta A, Hosseini SMA, Mehrazine M, Bandarian F. Craniopharyngioma: a clinicopathological study of 141 cases. *Endocr Pathol*. 2004;15:339–344.
34. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. *Hum Mutat*. 2008;29:22–32.
35. Agarwal SK, Beth Kester M, Debelenko LV, et al. Germline mutations of the MEN1 gene in familial multiple endocrine neoplasia type 1 and related states. *Hum Mol Genet*. 1997;6:1169–1175.
36. Guru SC, Prasad NB, Shin EJ, et al. Characterization of a MEN1 ortholog from Drosophila melanogaster. *Gene*. 2001;263:31–38.
37. Guru SC, Crabtree JS, Brown KD, et al. Isolation, genomic organization, and expression analysis of MEN1, the murine homolog of the MEN1 gene. *Mamm Genome*. 1999;10:592–596.
38. Stewart C, Parente F, Piehl F, et al. Characterization of the mouse MEN1 gene and its expression during development. *Oncogene*. 1998;17:2485–2493.
39. Sabetkish S, Kajbafzadeh AM, Sabetkish N, et al. Whole-organ tissue engineering: decellularization and recellularization of three-dimensional matrix liver scaffolds. *J Biomed Mater Res A*. 2015;103:1498–1508.
40. Wu Y, Feng Z-J, Gao S-B, et al. Interplay between menin and K-Ras in regulating lung adenocarcinoma. *J Biol Chem*. 2012;287:40003–40011.
41. Gao S-B, Feng Z-J, Xu B, et al. Suppression of lung adenocarcinoma through menin and polycomb gene-mediated repression of growth factor pleiotrophin. *Oncogene*. 2009;28:4095–4104.
42. Seigne C, Fontanière S, Carreira C, et al. Characterisation of prostate cancer lesions in heterozygous MEN1 mutant mice. *BMC Cancer*. 2010;10:395.
43. Seigne C, Auret M, Treilleux I, et al. High incidence of mammary intraepithelial neoplasia development in MEN1-disrupted murine mammary glands. *J Pathol*. 2013;229:546–558.
44. Karnik SK, Chen H, McLean GW, et al. Menin controls growth of pancreatic β-cells in pregnant mice and promotes gestational diabetes mellitus. *Science*. 2007;318:806–809.
45. Yang Y, Gurung B, Wu T, Wang H, Stoffers DA, Hua X. Reversal of preexisting hyperglycemia in diabetic mice by acute deletion of the MEN1 gene. *Proc Natl Acad Sci U S A*. 2010;107:20358–20363.
46. Yang Y, Wang H, Hua X. Deletion of the MEN1 gene prevents streptozotocin-induced hyperglycemia in mice. *Exp Diabetes Res*. 2010;2010:876701.
47. Aziz A, Miyake T, Engleka KA, Epstein JA, McDermott JC. Menin expression modulates mesenchymal cell commitment to the myogenic and osteogenic lineages. *Dev Biol*. 2009;332:116–130.
48. Hendy G, Kaji H, Sowa H, Lebrun J-J, Canaff L. Menin and TGF-β superfamily member signaling via the Smad pathway in pituitary, parathyroid and osteoblast. *Horm Metab Res*. 2005;37:375–379.
49. Inoue Y, Hendy G, Canaff L, Seino S, Kaji H. Menin interacts with β-catenin in osteoblast differentiation. *Horm Metab Res*. 2011;43:183–187.
50. Cheng P, Yang SS, Hu XG, et al. Menin prevents liver steatosis through co-activation of peroxisome proliferator-activated receptor alpha. *FEBS Lett*. 2011;585:3403–3408.
51. Kaji H. Menin and bone metabolism. *J Bone Miner Metab*. 2012;30:381–387.
52. Naito J, Kaji H, Sowa H, Hendy GN, Sugimoto T, Chihara K. Menin suppresses osteoblast differentiation by antagonizing the AP-1 factor, JunD. *J Biol Chem*. 2005;280:4785–4791.
53. Sowa H, Kaji H, Hendy GN, et al. Menin is required for bone morphogenetic protein 2-and transforming growth factor β-regulated osteoblastic differentiation through interaction with Smads and Runx2. *J Biol Chem*. 2004;279:40267–40275.
54. Zindy PJ, L'Helgoualc'h A, Bonnier D, et al. Upregulation of the tumor suppressor gene menin in hepatocellular carcinomas and its significance in fibrogenesis. *Hepatology*. 2006;44:1296–1307.
55. Wu T, Zhang X, Huang X, Yang Y, Hua X. Regulation of cyclin B2 expression and cell cycle G2/m transition by menin. *J Biol Chem*. 2010;285:18291–18300.
56. Omidfar K, Moinfar Z, Sohi AN, et al. Expression of EGFRvIII in thyroid carcinoma: immunohistochemical study by camel antibodies. *Immunol Invest*. 2009;38:165–180.
57. Huang J, Gurung B, Wan B, et al. The same pocket in menin binds both MLL and JUND but has opposite effects on transcription. *Nature*. 2012;482:542–546.
58. Hernandez J, Floyd D, Weilbaecher K, Green P, Boris-Lawrie K. Multiple facets of junD gene expression are atypical among AP-1 family members. *Oncogene*. 2008;27:4757–4767.
59. Agarwal SK, Novotny EA, Crabtree JS, et al. Transcription factor JunD, deprived of menin, switches from growth suppressor to growth promoter. *Proc Natl Acad Sci U S A*. 2003;100:10770–10775.
60. Saffar H, Sanii S, Heshmat R, et al. Expression of galectin-3, nm-23, and cyclooxygenase-2 could potentially discriminate between benign and malignant pheochromocytoma. *Am J Clin Pathol*. 2011;135:454–460.
61. Heppner C, Bilimoria KY, Agarwal SK, et al. The tumor suppressor protein menin interacts with NF-kB proteins and inhibits NF-kB-mediated transactivation. *Oncogene*. 2001;20:4917–4925.
62. Gurung B, Feng Z, Iwamoto DV, et al. Menin epigenetically represses Hedgehog signaling in MEN1 tumor syndrome. *Cancer Res*. 2013;73:2650–2658.
63. Luzi E, Marini F, Tognarini I, Galli G, Falchetti A, Brandi ML. The regulatory network menin-microRNA 26a as a possible target for RNA-based therapy of bone diseases. *Nucleic Acid Ther*. 2012;22:103–108.
64. Matkar S, Thiel A, Hua X. Menin: a scaffold protein that controls gene expression and cell signaling. *Trends Biochem Sci*. 2013;38:394–402.
65. Kaji H, Canaff L, Lebrun J-J, Goltzman D, Hendy GN. Inactivation of menin, a Smad3-interacting protein, blocks transforming growth factor type β signaling. *Proc Natl Acad Sci U S A*. 2001;98:3837–3842.
66. Chen G, Jingbo A, Wang M, et al. Menin promotes the Wnt signaling pathway in pancreatic endocrine cells. *Mol Cancer Res*. 2008;6:1894–1907.
67. Kim Y, Burns A, Goldsmith P, et al. Stable overexpression of MEN1 suppresses tumorigenicity of RAS. *Oncogene*. 1999;18:5936–5942.
68. Feng Z, Gao S, Wu Y, Xu X, Hua X, Jin G. Lung cancer cell migration is regulated via repressing growth factor PTN/RPTP β/ζ signaling by menin. *Oncogene*. 2010;29:5416–5426.
69. Gallo A, Cuozzo C, Esposito I, et al. Menin uncouples Elk-1, JunD and c-Jun phosphorylation from MAP kinase activation. *Oncogene*. 2002;21:6434–6445.
70. Wang Y, Ozawa A, Zaman S, et al. The tumor suppressor protein menin inhibits AKT activation by regulating its cellular localization. *Cancer Res*. 2010;71:371–382.
71. Wuescher L, Angevine K, Hinds T, Ramakrishnan S, Najjar SM, Mensah-Osman EJ. Insulin regulates menin expression, cytoplasmic localization, and interaction with FOXO1. *Am J Physiol Endocrinol Metab*. 2011;301:E474–E483.
72. Wu T, Hua X. Menin represses tumorigenesis via repressing cell proliferation. *Am J Cancer Res*. 2011;1:726–739.
73. Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*. 2012;97:2990–3011.
74. Pellegata NS, Quintanilla-Martinez L, Siggelkow H, et al. Germ-line mutations in p27Kip1 cause a multiple endocrine neoplasia syndrome in rats and humans. *Proc Natl Acad Sci U S A*. 2006;103:15558–15563.
75. Nightingale K. Epigenetic gene regulation. *Med Biotechnol*. 2009;45:97–115.
76. Hermann A, Gowher H, Jeltsch A. Biochemistry and biology of mammalian DNA methyltransferases. *Cell Mol Life Sci*. 2004;61:2571–2587.
77. Fontanière S, Duvillié B, Scharfmann R, Carreira C, Wang Z-Q, Zhang C-X. Tumour suppressor menin is essential for development of the pancreatic endocrine cells. *J Endocrinol*. 2008;199:287–298.
78. Vasavada RC, Gonzalez-Pertusa JA, Fujinaka Y, Fiaschi-Taesch N, Cozar-Castellano I, Garcia-Ocaña A. Growth factors and beta cell replication. *Int J Biochem Cell Biol*. 2006;38:931–950.
79. Yoshino A, Katayama Y, Ogino A, et al. Promoter hypermethylation profile of cell cycle regulator genes in pituitary adenomas. *J Neurooncol*. 2007;83:153–162.
80. Bello MJ, De Campos JM, Isla A, Casartelli C, Rey JA. Promoter CpG methylation of multiple genes in pituitary adenomas: frequent involvement of caspase-8. *Oncol Rep*. 2006;15:443–448.
81. Khatami F, Larijani B, Heshmat R, et al. Meta-analysis of promoter methylation in eight tumor-suppressor genes and its association with the risk of thyroid cancer. *PLoS ONE*. 2017;12:e0184892.
82. Khatami F, Noorinayer B, Ghiasi S, Mohebi R, Hashemi M, Zali MR. Single nucleotide polymorphisms of DNA methyltransferase 1 gene and gastric cancer in Iranian patients: a case control study. *Iran J Cancer Prev*. 2012;1:111–118.
83. Khatami F, Larijani B, Tavangar SM. Circulating tumor BRAF mutation and personalized thyroid cancer treatment. *Asian Pac J Cancer Prev*. 2017;18:293–294.
84. Chung YJ, Hwang S, Jeong JJ, Song SY, Kim SH, Rhee Y. Genetic and epigenetic analysis in Korean patients with multiple endocrine neoplasia type 1. *Endocrinol Metabo*. 2014;29:270–279.
85. Modigliani E, Vasen H, Raue K, et al. Pheochromocytoma in multiple endocrine neoplasia type 2: European study. *J Intern Med*. 1995;238:363–367.
86. Mulligan L, Ponder B. Genetic basis of endocrine disease: multiple endocrine neoplasia type 2. *J Clin Endocrinol Metab*. 1995;80:1989–1995.
87. Donis-Keller H, Dou S, Chi D, et al. Mutations in the RET proto-oncogene are associated with MEN 2A and FMTC. *Hum Mol Genet*. 1993;2:851–856.
88. Attaran S, Omrani G, Tavangar S. Lymphoepithelial-like intrathyroidal thymic carcinoma with foci of squamous differentiation. *APMIS*. 1996;104:419–423.

89. Marquard J, Ecmentsujiam Ardinger HH, Pagon RA, et al, eds. *GeneReviews®*. Seattle, WA: University of Washington, Seattle; 1993–2017. https://www.ncbi.nlm.nih.gov/books/NBK1257/.
90. Hofstra RM, Landsvater RM, Ceccherini I, et al. A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. *Nature*. 1994;367:375–376.
91. Neumann HP, Vortmeyer A, Schmidt D, et al. Evidence of MEN-2 in the original description of classic pheochromocytoma. *N Engl J Med*. 2007;357:1311–1315.
92. Sipple JH. Multiple endocrine neoplasia type 2 syndromes: historical perspectives. *Henry Ford Hosp Med J*. 1984;32:219–221.
93. Doppman J, Wells JRS, Buja LM. Sipple's syndrome: medullary thyroid carcinoma, pheochromocytoma, and parathyroid disease. *Ann Intern Med*. 1973;78:561–579.
94. Sanii S, Tavangar SM. Cutaneous metastasis of medullary thyroid carcinoma as the initial manifestation of an otherwise limited malignancy: a case report. *Am J Dermatopathol*. 2011;33:716–718.
95. Haghpanah V, Lashkari A, Moradzadeh K, Tavangar SM. Hypereosinophilia as the presentation of metastatic medullary thyroid carcinoma: a remarkable event. *Am J Med Sci*. 2007;334:131–132.
96. Asari R, Scheuba C, Kaczirek K, Niederle B. Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A. *Arch Surg*. 2006;141:1199–1205.
97. Khatami F, Tavangar SM. Current diagnostic status of pheochromocytoma and future perspective: a mini review. *Iran J Pathol*. 2017;12:313–322.
98. Amousha MRH, Kish NS, Heshmat R, et al. Corrigendum: expression of the pituitary tumor transforming gene (PTTG1) in pheochromocytoma as a potential marker for distinguishing benign versus malignant tumors. *Acta Med Iran*. 2015;53:392.
99. Howe J, Norton J, Wells S. Prevalence of pheochromocytoma and hyperparathyroidism in multiple endocrine neoplasia type 2A: results of long-term follow-up. *Surgery*. 1993;114:1070–1077.
100. Verdy M, Weber AM, Roy CC, Morin CL, Cadotte M, Brochu P. Hirschsprung's disease in a family with multiple endocrine neoplasia type 2. *J Pediatr Gastroenterol Nutr*. 1982;1:603–608.
101. Verdy M, Cadotte M, Schurch W, et al. A French Canadian family with multiple endocrine neoplasia type 2 syndromes. *Henry Ford Hosp Med J*. 1983;32:251–253.
102. Eng C, Clayton D, Schuffenecker I, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2: international RET mutation consortium analysis. *JAMA*. 1996;276:1575–1579.
103. Datcu M, Datcu G, Fermeşanu I, Aursulesei V. Pheochromocytoma—late diagnosis after subarachnoid hemorrhage. *Acta Endocrinol*. 2009;5:265.
104. Leboulleux S, Baudin E, Travagli JP, Schlumberger M. Medullary thyroid carcinoma. *Clin Endocrinol*. 2004;61:299–310.
105. Kajbafzadeh A-M, Payabvash S, Salmasi AH, Monajemzadeh M, Tavangar SM. Smooth muscle cell apoptosis and defective neural development in congenital ureteropelvic junction obstruction. *J Urol*. 2006;176:718–723.
106. Tavangar SM, Shojaee A, Tabriz HM, et al. Immunohistochemical expression of Ki67, c-erbB-2, and c-kit antigens in benign and malignant pheochromocytoma. *Pathol Res Pract*. 2010;206:305–309.
107. Khatami F, Tavangar S. Genetic and epigenetic of medullary thyroid cancer. *Iran Biomed J*. 2018;22:142–150.
108. Sabetkish N, Tavangar SM. An unusual combination of parathyroid adenoma, medullary and papillary thyroid carcinoma. *Acta Med Iran*. 2013;51:337–340.
109. Gagel RF. Medullary thyroid carcinoma. *Pediatr Oncol*. 2005:167–179.
110. Kouvaraki MA, Shapiro SE, Fornage BD, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery*. 2003;134:946–954.
111. Kloos R, Eng C, Evans D, et al. American Thyroid Association Guidelines. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009;19:565–612.
112. Cohen M, Moley J. Surgical treatment of medullary thyroid carcinoma. *J Intern Med*. 2003;253:616–626.
113. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: the American Thyroid Association Guidelines Task Force on medullary thyroid carcinoma. *Thyroid*. 2015;25:567–610.
114. Machens A, Niccoli-Sire P, Hoegel J, et al. Early malignant progression of hereditary medullary thyroid cancer. *N Engl J Med*. 2003;349:1517–1525.
115. Yip L, Cote GJ, Shapiro SE, et al. Multiple endocrine neoplasia type 2: evaluation of the genotype-phenotype relationship. *Arch Surg*. 2003;138:409–416.
116. Erlic Z, Hoffmann MM, Sullivan M, et al. Pathogenicity of DNA variants and double mutations in multiple endocrine neoplasia type 2 and von Hippel-Lindau syndrome. *J Clin Endocrinol Metab*. 2010;95:308–313.
117. Asa SL. How familial cancer genes and environmentally induced oncogenes have changed the endocrine landscape. *Mod Pathol*. 2001;14:246–253.
118. Mulligan LM. RET revisited: expanding the oncogenic portfolio. *Nat Rev Cancer*. 2014;14:173–186.
119. Nakamura T, Ishizaka Y, Nagao M, Hara M, Ishikawa T. Expression of the ret proto-oncogene product in human normal and neoplastic tissues of neural crest origin. *J Pathol*. 1994;172:255–260.
120. Santoro M, Rosati R, Grieco M, et al. The RET proto-oncogene is consistently expressed in human pheochromocytomas and thyroid medullary carcinomas. *Oncogene*. 1990;5:1595–1598.
121. Pachnis V, Mankoo B, Costantini F. Expression of the c-ret proto-oncogene during mouse embryogenesis. *Development*. 1993;119:1005–1017.
122. Andrew SD, Capes-Davis A, Delhanty PJ, Marsh DJ, Mulligan LM, Robinson BG. Transcriptional repression of the RET proto-oncogene by a mitogen activated protein kinase-dependent signalling pathway. *Gene*. 2002;298:9–19.
123. Leon TY, Ngan ES, Poon H-C, et al. Transcriptional regulation of RET by Nkx2-1, Phox2b, Sox10, and Pax3. *J Pediatr Surg*. 2009;44:1904–1912.
124. Lang D, Epstein JA. Sox10 and Pax3 physically interact to mediate activation of a conserved c-RET enhancer. *Hum Mol Genet*. 2003;12:937–945.
125. Sarmadi S, Izadi-Mood N, Sotoudeh K, Tavangar SM. Altered PTEN expression; a diagnostic marker for differentiating normal, hyperplastic and neoplastic endometrium. *Diagn Pathol*. 2009;4:41.
126. Myers SM, Eng C, Ponder B, Mulligan LM. Characterization of RET proto-oncogene 3′ splicing variants and polyadenylation sites: a novel C-terminus for RET. *Oncogene*. 1995;11:2039–2045.
127. Tahira T, Ishizaka Y, Itoh F, Sugimura T, Nagao M. Characterization of ret proto-oncogene mRNAs encoding two isoforms of the protein product in a human neuroblastoma cell line. *Oncogene*. 1990;5:97–102.
128. Carter M, Yome J, Marcil M, Martin C, Vanhorne J, Mulligan L. Conservation of RET proto-oncogene splicing variants and implications for RET isoform function. *Cytogenet Cell Genet*. 2001;95:169–176.
129. Anders J, Kjær S, Ibáñez CF. Molecular modeling of the extracellular domain of the RET receptor tyrosine kinase reveals multiple cadherin-like domains and a calcium-binding site. *J Biol Chem*. 2001;276:35808–35817.
130. Kjær S, Hanrahan S, Totty N, McDonald NQ. Mammal-restricted elements predispose human RET to folding impairment by HSCR mutations. *Nat Struct Mol Biol*. 2010;17:726–731.
131. Amoresano A, Incoronato M, Monti G, Pucci P, de Franciscis V, Cerchia L. Direct interactions among Ret, GDNF and GFRα1 molecules reveal new insights into the assembly of a functional three-protein complex. *Cell Signal*. 2005;17:717–727.
132. Wang X. Structural studies of GDNF family ligands with their receptors—insights into ligand recognition and activation of receptor tyrosine kinase RET. *Biochim Biophys Acta*. 2013;1834:2205–2212.
133. Richardson DS, Rodrigues DM, Hyndman BD, Crupi MJ, Nicolescu AC, Mulligan LM. Alternative splicing results in RET isoforms with distinct trafficking properties. *Mol Biol Cell*. 2012;23:3838–3850.
134. Runeberg-Roos P, Virtanen H, Saarma M. RET (MEN 2B) is active in the endoplasmic reticulum before reaching the cell surface. *Oncogene*. 2007;26:7909–7915.
135. Arighi E, Borrello MG, Sariola H. RET tyrosine kinase signaling in development and cancer. *Cytokine Growth Factor Rev*. 2005;16:441–467.
136. Sanicola M, Hession C, Worley D, et al. Glial cell line-derived neurotrophic factor-dependent RET activation can be mediated by two different cell-surface accessory proteins. *Proc Natl Acad Sci U S A*. 1997;94:6238–6243.
137. Kihara M, Miyauchi A, Yoshioka K, et al. Germline RET mutation carriers in Japanese patients with apparently sporadic medullary thyroid carcinoma: a single institution experience. *Auris Nasus Larynx*. 2016;43:551–555.
138. Santoro M, Carlomagno F, Romano A, Bottaro DP. Activation of RET as a dominant transforming gene by germline mutations of MEN2A and MEN2B. *Science*. 1995;267:381–383.
139. Mulligan LM, Eng C, Healey CS, et al. Specific mutations of the RET proto-oncogene are related to disease phenotype in MEN 2A and FMTC. *Nat Genet*. 1994;6:70–74.
140. Eng C. The RET proto-oncogene in multiple endocrine neoplasia type 2 and Hirschsprung's disease. *N Engl J Med*. 1996;335:943–951.
141. Gestblom C, Sweetser DA, Doggett B, Kapur RP. Sympathoadrenal hyperplasia causes renal malformations in Ret MEN2B-transgenic mice. *Am J Pathol*. 1999;155:2167–2179.
142. Valdés N, Navarro E, Mesa J, et al. RET Cys634Arg mutation confers a more aggressive multiple endocrine neoplasia type 2A phenotype than Cys634Tyr mutation. *Eur J Endocrinol*. 2015;172:301–307.
143. Eng C, Smith DP, Mulligan LM, et al. Point mutation within the tyrosine kinase domain of the RET proto-oncogene in multiple endocrine neoplasia type 2B and related sporadic tumours. *Hum Mol Genet*. 1994;3:237–241.

144. Valente F, Dias da Silva MR, Camacho C, et al. Comprehensive analysis of RET gene should be performed in patients with multiple endocrine neoplasia type 2 (MEN 2) syndrome and no apparent genotype-phenotype correlation: an appraisal of p. Y791F and P. C634Y RET mutations in five unrelated Brazilian families. *J Endocrinol Invest*. 2013;36:975–981.
145. Fetz A, Crupi MJ, Lian E, Hyndman BD, Mulligan LM. The RET receptor Y791F variant activates the kinase but diminishes ligand responsiveness. *AACR*. 2015;75:Abstract: 4990.
146. Qi X-P, Zhao J, Du Z, et al. Prophylactic thyroidectomy for MEN 2-related medullary thyroid carcinoma based on predictive testing for RET proto-oncogene mutation and basal serum calcitonin in China. *Eur J Surg Oncol*. 2013;39:1007–1012.
147. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. *Nat Rev Genet*. 2002;3:415–428.
148. Dammann R, Schagdarsurengin U, Seidel C, et al. Frequent promoter methylation of tumor-related genes in sporadic and men2-associated pheochromocytomas. *Exp Clin Endocrinol Diabet*. 2005;113:1–7.
149. Schagdarsurengin U, Gimm O, Hoang-Vu C, Dralle H, Pfeifer GP, Dammann R. Frequent epigenetic silencing of the CpG island promoter of RASSF1A in thyroid carcinoma. *Cancer Res*. 2002;62:3698–3701.
150. Brait M, Loyo M, Rosenbaum E, et al. Correlation between BRAF mutation and promoter methylation of TIMP3, RARβ2 and RASSF1A in thyroid cancer. *Epigenetics*. 2012;7:710–719.
151. Mohammadi-asl J, Larijani B, Khorgami Z, et al. Qualitative and quantitative promoter hypermethylation patterns of the P16, TSHR, RASSF1A and RARβ2 genes in papillary thyroid carcinoma. *Med Oncol*. 2011;28: 1123–1128.