REVIEW ARTICLE

MEN 5: The New Kid on the Block—A Comprehensive Narrative Review

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Abstract

In addition to the recognized types of multiple endocrine neoplasia (MEN) syndromes (MEN 1, MEN 2a, and MEN 2b), MEN 4 was described relatively recently, and there is now a proposition of a fifth variety. It has been recognized as an independent syndrome by the 5th edition of the WHO Classification of Endocrine and Neuroendocrine Tumors as well as the 5th edition of the Genetic Tumor Syndromes. Multiple endocrine neoplasia type 5 (MEN 5) is caused by a pathogenic mutation in *MYC associated factor X (MAX)* gene, which is a tumor suppressor gene. The endocrine manifestations include tumors of the adrenal, pituitary, parathyroid, and pancreas. The non-endocrine tumors include renal cell carcinoma, renal oncocytoma, and carcinoma of the lung. This article thoroughly reviews the available literature and tries to understand the journey of discovery of a new syndrome in endocrine surgery.

Keywords: MEN 5, Multiple endocrine neoplasia, Paraganglioma, Pheochromocytoma, Pituitary adenoma.

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Introduction

Multiple endocrine neoplasia type 5 (MEN 5) finds a place in the 5th edition of the WHO classification of Endocrine and Neuroendocrine tumors as well as the 5th edition of the Genetic Tumor Syndromes as a separate novel entity. As per the current knowledge, it is caused by a pathogenic mutation in *MYC associated factor X (MAX)* gene, which is a tumor suppressor gene. This syndrome is characterized by multifocal neoplasms in various endocrine and non-endocrine organs. The endocrine manifestations include tumors of the adrenal, pituitary, parathyroid, and pancreas. The non-endocrine tumors include renal cell carcinoma, renal oncocytoma, and carcinoma of the lung.

In addition to the recognized types of MEN syndromes (MEN 1, MEN 2a, and MEN 2b), MEN 4 was described relatively recently, and there is now a proposition of a fifth variety. We have reviewed the current literature on this new syndrome alongside shedding light on how the syndrome was discovered and further researched.

There is a paucity of literature, but we have done our best to collaborate the relevant literature to give the reader an insight into the journey of the discovery phase of a novel syndrome. Thus, this review begins with a discussion on how different pathologies of different organs were zeroed in on a single entity, followed by the pathogenesis of the syndrome. This then delves into the presentation and organ involvement, pathological features, and management.

Journey of Discovery of the Syndrome

The research on the new syndrome began with a quest to characterize a subset of pheochromocytoma (PCC) and paragangliomas (PGLs) that presented similarly as the syndromic cases, that is with positive family history, young age at presentation, bilateral involvement, or multiple synchronous or metachronous lesions. MYC-associated factor X mutation was identified in these individuals and a paternal transmission with uniparental disomy was apparent.[1] This study was done as a follow-up after an exome sequencing study discovered a novel gene in hereditary PCC in 5 out of the 59 cases sequenced.[2] MYC-associated factor X mutation accounted for 1.12% of cases of PCC/PGL which were negative for the six common susceptibility genes [including von Hippel-Lindau (VHL), rearranged during transfection (RET), and succinate dehydrogenase (SDH)]. It was also seen in 1.65% of the sporadic cases. This indirectly highlighted the role of the *MAX* gene in the pathogenesis of neural crest tumors. The dysregulation of the MYC pathway, which is related to the MAX mutation has an established role in the development of neuroblastoma.[3] That same dysregulation was suspected in these cases of PCC/PGL. This was followed by several case reports of synchronous, metachronous, or multiple PCC/PGL with MAX mutation.[4,5] The interest in the syndromic involvement was further deepened with a report of a patient with pituitary prolactinoma and bilateral PCC, alongside mild primary hyperparathyroidism (PHPT).[6] This was followed by a case series of three such patients with PCC and pituitary adenoma with germline MAX mutation which was heterogeneous and in the exon region.[7] One patient had a right PCC and several years later, presented with galactorrhea. Another patient had growth hormone-secreting pituitary microadenoma with bilateral PCC. On follow-up, this patient was diagnosed with a follicular variant of papillary thyroid carcinoma as well. The third case presented with acromegaly at 16 years, unilateral PCC at 22 years, and contralateral PCC after 11 years.[7] This article highlights the immense importance of patient follow-up and data keeping in endocrine surgery which led to the decoding

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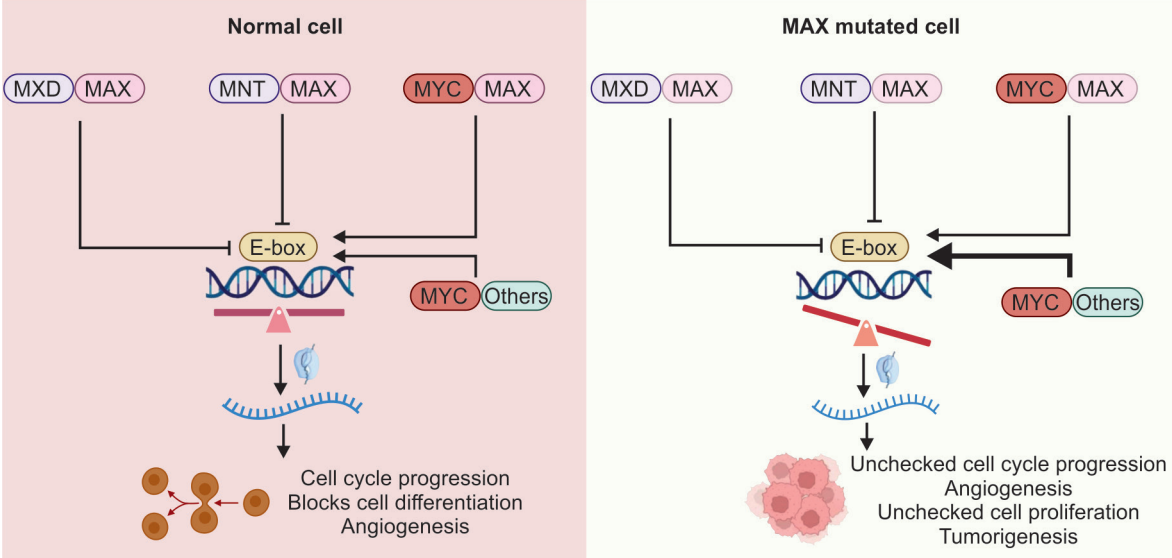

Fig. 1: The left side depicts the functioning of the MAX-MYC-MXD axis in a normal cell. MAX is a basic, helix-loop-helix protein that binds to the E-box sequence of the DNA after the formation of heterodimers with either MYC or MXD/MNT. These dimers either promote or repress the transcription. With its partner MAX and either activates or represses transcription. MYC is also activated by other factors and in a normal cell, a critical balance is maintained. MYC and MAX regulate cell cycle progression, genomic instability, and other such processes. Thus, the cell undergoes controlled division. In comparison, as shown on the right side is the cell with mutated MAX gene. In this situation, alternate pathways of MYC activation act as the dominant driving force for the overexpression of MYC and the balance is disturbed. This leads to rapid cell cycle progression, angiogenesis, and in turn tumorigenesis

of the infamous "3 PA syndrome," constituting pituitary adenomas, PCC, and PGL, which were SDHx negative.[8]

The association grew stronger with another case report published in 2020 of a young patient with recurrent PCC and ganglioneuromas with MAX mutation.[9] At the same time, another report from Belgium described a low-grade pancreatic neuroendocrine neoplasm in a patient born to the father with a known MAX mutation.[10] However, the unequivocal association was made by the landmark paper by Seabrook. et al in 2021, which reported two families with germline MAX variants with multiple endocrine and neuroendocrine tumors, proposing it to be the causative mutation for the 5th type of MEN.[11] A systematic review that was done for the MAX gene-associated neoplasms yielded 37 articles with 113 patients with germline MAX mutation.[12]

The salient takeaway point from this brief historical progression is the importance of keeping a high suspicion in the cases that present at a young age with endocrine tumors, especially when they test negative for the known mutations. The eyes see what the mind knows and the more the mind will know the more these eyes will see and decode.

Epidemiology

Owing to its recent description, there is a lack of robust data on the incidence and prevalence of this syndrome. However, based on the data of PCC, pathogenic MAX mutation is seen in less than 1% of all the cases.[1] The median age at diagnosis of PCC is 34 years and that of presentation of the first tumor is 28.5 years (IQR, 22–38.3 years).[12,13] No gender predilection is reported with about 1:1 male-to-female ratio.[11,12]

Etiology

Multiple endocrine neoplasia type 5 syndrome is attributed to the pathogenic germline mutations in the *MAX* gene, which is located on chromosome 14q23.3. MYC-associated factor X is a tumor suppressor gene that encodes a component of the transcription factor that participates in cell proliferation, differentiation, and apoptosis.[2,14] There have been missense, nonsense, as well as deletion mutations that contributed to the pathogenic variant.[1,2,7,13,15] The next section discusses the pathogenesis of this syndrome.

Pathogenesis

The pathogenesis of the syndrome is complex, and we have attempted to explain it more simply. The hallmark of tumor development lies in the unchecked proliferation of the cells that escape the normal regulatory mechanisms. These regulatory mechanisms are encoded by the tumor suppressor genes and those which promote cell growth act as the oncogenes. The oncogene in these tumors is the *myelocytomatosis oncogene (myc) gene* which encodes for the protein MYC. MYC promotes transcription by binding to a certain region of the DNA. Thus, a cell in proliferation requires MYC expression, as depicted in Figure 1.[2] The overexpression of MYC has been associated with several malignancies in humans.[16] Another pathway promoting cell growth is through the receptor tyrosine kinase RET. When triggered it activates the PIK3CA signaling by recruiting IRS proteins. This complex further activates AKT which phosphorylates and activates the mTOR and mTOR further activates the phosphorylated S6K1 which mediates its action via S6 which promotes cell growth and proliferation, as shown in Figure 2. This cell in proliferation requires MYC expression. The overexpression of this MYC leads to tumorigenesis by activating the transcription of genes responsible for cell proliferation and angiogenesis and repressing the genes responsible for cell differentiation.[17] Also, MYC and mTOR are independent pathways that lead to cell proliferation, and we are aware of the other syndromes that are caused due to mutation in the *RET* gene (MEN 2). However, there are reports of

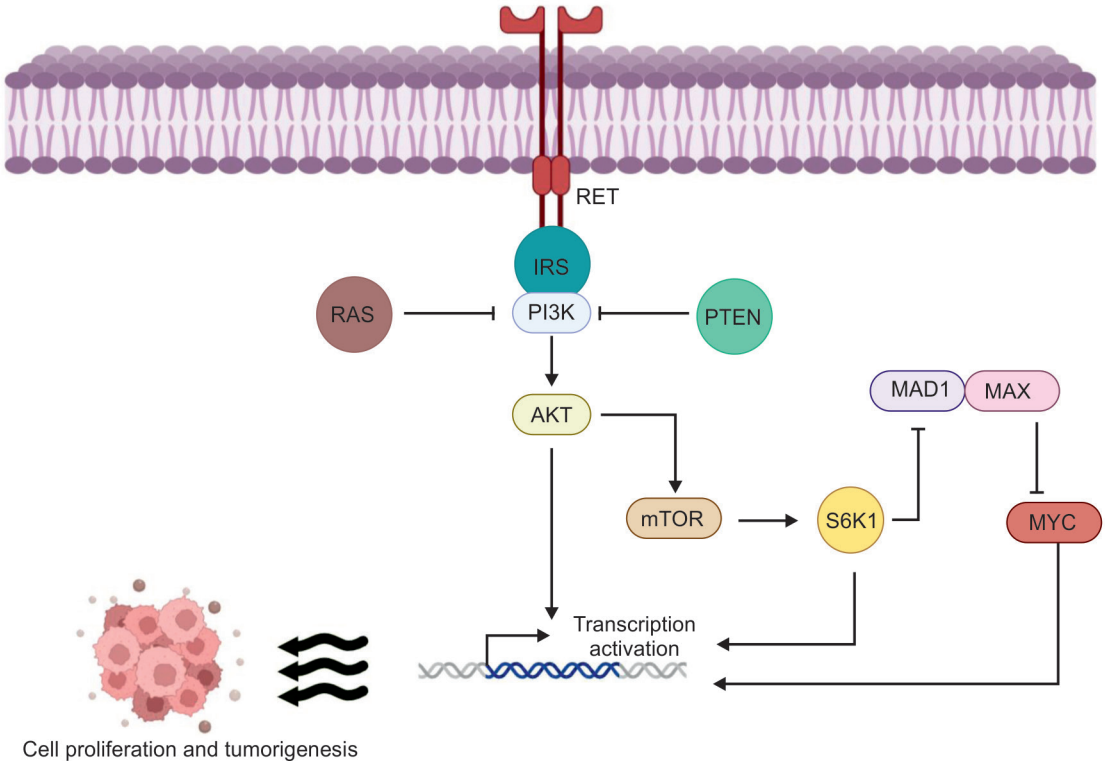

Fig. 2: Cross-talk between the two pathways. RET/PIK3CA/mTOR mediates the downward signaling of cell processes such as cell growth regulation, cell division, and cell survival. Thus, when mutated leads to unchecked proliferation and tumorigenesis. The downward activation via several steps leads to the activation of S6K1, which mediates the actions further downstream for transcription activation. In addition to this, it also inhibits the action of MAD1/MAX heterodimers, which inhibit the MYC-mediated transcription, thus indirectly promoting MYC overexpression

cross-talk between the RAS-PIK3CA-mTOR and MYC-MAX pathways, as shown in Figure 2.[18]

MYC-associated factor X is a constitutively expressed protein present ubiquitously with a central role in the regulation of MYC expression. *MYC-associated factor X* gene has 5 exons and mutation can be seen in anyone but is more frequent on exons 3 and 4.[2] MYC-associated factor X plays a dual role in the activation and inhibition of MYC expression. MYC-associated factor X heterodimerizes with the *MYC* gene, binds to the target DNA of the genes, and promotes their transcription. This binding is mediated by the basic helix-loop-helix leucine zipper (bHLHZip) domain of the MAX protein. This is a highly conserved sequence of amino acids and thus, any mutation in this leads to the inability of the MAX protein to bind to DNA and other proteins.[16,19] The second role, and the major clinically relevant role of MAX protein is to make heterodimers with a family of proteins called MAX dimerization protein (MXD). It includes MXD1, MXD3, and MXD4. The other proteins are MAX-binding protein (MNT) and MAX gene-associated protein (MGA). These dimers repress the transcription through the E-box DNA recognition sequences which are usually activated by MYC and hence, lead to anti-tumorigenesis.[16,20] Biologically it has been shown that this repression of MYC by the MAX-mediated heterodimers is the dominant action than the promotion of MYC expression.[21]

The exome sequencing revealed a germline mutation with loss of heterozygosity (LOH), which suggested that MAX acts as a tumor suppressor gene.[2] The LOH in a few cases has been reported due to the uniparental disomy with maternal allele silencing.[2] This method of transmission usually results in generation-skipping and complicates the identification of mutation carriers. Thus, the constitutional loss of function leads to unchecked MYC overexpression causing malignancies, as shown in Figure 1. This also highlights the possibility of the MYC-MAX-MXD1 pathway as a common terminal pathway for tumorigenesis of PGL for other susceptibility genes as well.[22]

Clinical Features

The clinical presentation encompasses both endocrine and non-endocrine tumors. The endocrine tumors include PCC/PGL, pituitary neuroendocrine tumors (PitNETs) or pituitary adenomas, pancreatic neuroendocrine neoplasms (PNENs), and multiglandular parathyroid adenomas.[11]

Pheochromocytomas in the patients of MEN 5 syndrome are bilateral in 63.4% of cases with equal rates of synchronous and asynchronous bilaterality. These patients can also have metachronous PGLs.[1,4,5,23] The rate of metastatic PCC/PGLs is 28%.[12] The presentation is classic with adrenergic crisis, hypertension, diaphoresis, and palpitations. The majority of these tumors are only norepinephrine producing (80%), followed by epinephrine and norepinephrine producing tumors and epinephrine only producing tumors. Table 1 summarizes the tumors associated with MEN 5 with their prevalence and the median age of presentation.

Multiple endocrine neoplasia type 5 associated PitNETs are normally functional, presenting with acromegaly, and/or hyperprolactinemia.[6,7] These tumors are typically diagnosed later than the PCC/PGL.[11] Although the recent systematic review of all the cases of MEN 5 syndrome reports that PitNETs were seen in 8% of

Table 1: The prevalence of the individual tumors in cases of MEN 5 with their age at onset[12]

Category of tumors	*Individual tumors*	*Percentage of the cases (113 reported cases)*	*Median age at presentation (IQR) (Years)*
Endocrine	Pheochromocytoma	87.6	28.5 (23–37.8)
	Paraganglioma	8	43 (32–46)
	Pituitary adenoma	8	31 (29.5–34.3)
	Parathyroid adenoma	3.5	NA
	Pancreatic NEN	0.8	NA
Non-endocrine	Ganglioneuroma	5.3	NA
	Neuroblastoma	5.3	NA
	Lung cancer	3.5	NA

IQR, interquartile range; NA, the cases are too few to report this statistic

the cases.[12] These patients can also have acromegaly due to other tumors (mixed PCC and ganglioneuroma) which secrete growth hormone-releasing hormone (GHRH).[11]

The patients also present with hypercalcemia which is either due to the multiglandular parathyroid adenomas or due to PTH or PTH-related peptide secretion from other tumors such as the PCC.[6] There are only 4 cases of MEN 5 with PHPT.[12] The PNEN is reported in only one case of MEN 5 syndrome.[10] There is a case described with the occurrence of a follicular variant of papillary thyroid cancer as well, but that tumor retained the MAX stain on immunohistochemistry.[7] The significance of this is discussed in the pathology section.

The non-endocrine manifestations include tumors of neural crest origin, such as ganglioneuroma and neuroblastoma, lung cancer, renal cell cancer, and renal oncocytoma in varied proportions.[11,15,24,25]

Diagnosis

The diagnosis should be suspected in cases with multiple tumors as discussed above. In addition to that the index of suspicion should be high in younger individuals with endocrine tumors and all the asymptomatic family members of known germline MAX mutation. These individuals should be subjected to genetic testing for further phenotypic characterization of MEN 5.

For clinching the diagnosis in an individual, the respective biochemical testing should be done for the individual tumors. This is followed by an appropriate imaging modality to localize the suspected tumor, as is done for the endocrine neoplasms routinely. Imaging with ^{18}F-FDOPA has been shown to be highly sensitive for localizing the PCC and PGLs both at diagnosis and follow-up. The ^{68}Ga-DOTATATE and FDG-PET are less sensitive in this setting.[13]

Management

This syndrome has been recently described, and the reported cases are limited thus the management is done for the sporadic cases as per the existing guidelines for the respective tumors. There are no current recommendations for any prophylactic surgical procedures or screening in individuals with known mutation of the *MAX* gene.

Pathology Features

Macroscopically and microscopically the tumors are indistinguishable from their sporadic counterparts. The only tendency that these tumors showcase is the multifocality/bilaterality. Some cases might have diffuse adrenal medullary hyperplasia as seen in MEN 2 syndrome and SDH deficient PGLs.[24,26] However, if this medullary proliferation is distinct and smaller than 10 mm, it is labeled as micro-PCC.[27]

The tumors from MEN 5 patients have been subjected to MAX immunohistochemistry to showcase the loss of staining. This occurs only in tumors with truncating mutations and thus, the sensitivity and specificity are poor.[1,2,11,28] Hence, it is not advised to use it as a screening test for the detection of MAX mutation in the absence of facilities for performing gene sequencing.[11]

Conclusion

MEN 5 is a novel syndrome caused due the pathogenic mutation in the *MAX* gene. It encompasses classic MEN-associated tumors such as PCC/PGL, pituitary, parathyroid, and pancreatic tumors along with nonendocrine tumors, such as those arising from the neural crest cells, renal cell carcinoma, and renal oncocytoma. A lifelong surveillance in subjects with pathogenic MAX variants is warranted.

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References

1. Burnichon N, Cascón A, Schiavi F, et al. MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. Clin Cancer Res 2012;18(10):2828–2837. DOI: 10.1158/1078-0432.CCR-12-0160.
2. Comino-Méndez I, Gracia-Aznárez FJ, Schiavi F, et al. Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. Nat Genet 2011;43(7):663–667. DOI: 10.1038/ng.861.
3. Kohl NE, Kanda N, Schreck RR, et al. Transposition and amplification of oncogene-related sequences in human neuroblastomas. Cell 1983;35(2):359–367. DOI: 10.1016/0092-8674(83)90169-1.
4. Ferrara AM, Lombardi G, Pambuku A, et al. Temozolomide treatment of a malignant pheochromocytoma and an unresectable MAX-related paraganglioma. Anticancer drugs 2018;29(1):102–105. DOI: 10.1097/CAD.0000000000000570.
5. Shibata M, Inaishi T, Miyajima N, et al. Synchronous bilateral pheochromocytomas and paraganglioma with novel germline mutation in MAX: A case report. Surg Cas Rep 2017;3:1–5. DOI: 10.1186/s40792-017-0408-x.
6. Roszko KL, Blouch E, Blake M, et al. Case report of a prolactinoma in a patient with a novel MAX mutation and bilateral pheochromocytomas. J Endocr Soc 2017;1(11):1401–1407. DOI: 10.1210/js.2017-00135.

7. Daly AF, Castermans E, Oudijk L, et al. Pheochromocytomas and pituitary adenomas in three patients with MAX exon deletions. Endocr Relat Cancer 2018;25(5):L37–L42. DOI: 10.1530/ERC-18-0065.
8. Xekouki P, Szarek E, Bullova P, et al. Pituitary adenoma with paraganglioma/pheochromocytoma (3PAs) and succinate dehydrogenase defects in humans and mice. J Clin Endocrin Metab 2015;100(5):E710–E719. DOI: 10.1210/jc.2014-4297.
9. Pozza C, Sesti F, Di Dato C, et al. A novel MAX gene mutation variant in a patient with multiple and "composite" neuroendocrine–neuroblastic tumors. Front Endocrinol 2020;11:234. DOI: 10.3389/fendo.2020.00234.
10. Petignot S, Daly AF, Castermans E, et al. Pancreatic neuroendocrine neoplasm associated with a familial MAX deletion. Horm Metab Res 2020;52(11):784–787. DOI: 10.1055/a-1186-0790.
11. Seabrook AJ, Harris JE, Velosa SB, et al. Multiple endocrine tumors associated with germline MAX mutations: Multiple endocrine neoplasia type 5? J Clin Endocrin Metab 2021;106(4):e1163–e1182. DOI: 10.1210/clinem/dgaa957.
12. Charoenngam N, Likasitwatanakul P, Kansuttiviwat C, et al. THU613 multiple endocrine neoplasia type 5 associated with germline max mutations—new insights into this proposed entity. J Endocr Soc 2023;7(Supplement_1):114–143. DOI: 10.1210/jendso/bvad114.143.
13. Taïeb D, Jha A, Guerin C, et al. 18F-FDOPA PET/CT imaging of MAX-related pheochromocytoma. J Clin Endocrin Metab 2018;103(4):1574–1582. DOI: 10.1210/jc.2017-02324.
14. Atchley WR, Fitch WM. Myc and Max: Molecular evolution of a family of proto-oncogene products and their dimerization partner. Proc Natl Acad Sci U S A 1995;92(22):10217–10221. DOI: 10.1073/pnas.92.22.10217.
15. Casey RT, Warren AY, Martin JE, et al. Clinical and molecular features of renal and pheochromocytoma/paraganglioma tumor association syndrome (RAPTAS): Case series and literature review. J Clin Endocrin Metab 2017;102(11):4013–4022. DOI: 10.1210/jc.2017-00562.
16. Cascón A, Robledo M. MAX and MYC: A heritable breakup. Cancer Res 2012;72(13):3119–3124. DOI: 10.1158/0008-5472.CAN-11-3891.
17. Berg T, Cohen SB, Desharnais J, et al. Small-molecule antagonists of Myc/Max dimerization inhibit Myc-induced transformation of chicken embryo fibroblasts. PNAS 2002;99(6):3830–3835. DOI: 10.1073/pnas.062036999.
18. Zhu J, Blenis J, Yuan J. Activation of PI3K/Akt and MAPK pathways regulates Myc-mediated transcription by phosphorylating and promoting the degradation of Mad1. Proc Natl Acad Sci U S A 2008;105(18):6584–6589. DOI: 10.1073/pnas.0802785105.
19. Nair SK, Burley SK. X-ray structures of Myc-Max and Mad-Max recognizing DNA: Molecular bases of regulation by proto-oncogenic transcription factors. Cell 2003;112(2):193–205. DOI: 10.1016/s0092-8674(02)01284-9.
20. Grandori C, Cowley SM, James LP, et al. The Myc/Max/Mad network and the transcriptional control of cell behavior. Annu Rev Cell Dev Biol 2000;16(1):653–699. DOI: 10.1146/annurev.cellbio.16.1.653.
21. Gallant P, Steiger D. Myc's secret life without Max. Cell Cycle 2009;8(23):3848–3853. DOI: 10.4161/cc.8.23.10088.
22. Qin N, De Cubas AA, Garcia-Martin R, et al. Opposing effects of HIF1α and HIF2α on chromaffin cell phenotypic features and tumor cell proliferation: Insights from MYC-associated factor X. Inter J cancer 2014;135(9):2054–2064. DOI: 10.1002/ijc.28868.
23. Bausch B, Schiavi F, Ni Y, et al. Clinical characterization of the pheochromocytoma and paraganglioma susceptibility genes SDHA, TMEM127, MAX, and SDHAF2 for gene-informed prevention. JAMA Oncol 2017;3(9):1204–1212. DOI: 10.1001/jamaoncol.2017.0223.
24. Korpershoek E, Koffy D, Eussen BH, et al. Complex MAX rearrangement in a family with malignant pheochromocytoma, renal oncocytoma, and erythrocytosis. J Clin Endocrin Metab 2016;101(2):453–460. DOI: 10.1210/jc.2015-2592.
25. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature 2014;511(7511):543. DOI: 10.1038/nature13385.
26. Grogan RH, Pacak K, Pasche L, et al. Bilateral adrenal medullary hyperplasia associated with an SDHB mutation. J Clin Oncol 2011;29(8):e200–e202. DOI: 10.1200/JCO.2010.32.2156.
27. Romanet P, Guerin C, Pedini P, et al. Pathological and genetic characterization of bilateral adrenomedullary hyperplasia in a patient with germline MAX mutation. Endocr Pathol 2017;28:302–307. DOI: 10.1007/s12022-016-9460-5.
28. Cheung VK, Gill AJ, Chou A. Old, new, and emerging immunohistochemical markers in pheochromocytoma and paraganglioma. Endocr pathol 2018;29:169–175. DOI: 10.1007/s12022-018-9534-7.