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Genetics of pheochromocytoma and paraganglioma syndromes: new advances and future treatment options

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Abstract

Purpose of review—To summarize the recent advances in the genetics of pheochromocytoma and paraganglioma (PHEO/PGL), focusing on the new susceptibility genes and dividing PHEOs/PGLs into two groups based on their transcription profile.

Recent findings—Recently, *TMEM127*, MYC-associated factor X, and hypoxia-inducible factor (HIF) 2 α have been described in the pathogenesis of PHEOs/PGLs. Thus, now about 30–40% of these tumors are linked to the germline mutations, which also include mutations in the *VHL*, *RET*, *NF1*, *SDHx*, and *SDHAF2* genes. Furthermore, PHEOs/PGLs have been divided into two groups, cluster 1 (SDHx/VHL) and cluster 2 (RET/NF1), based on the transcription profile revealed by genome-wide expression microarray analysis.

Summary—PHEOs/PGLs are the most inherited tumors among (neuro)endocrine tumors. Future approaches in genetics, including whole-genome sequencing, will allow the discovery of additional PHEO/PGL susceptibility genes. The current division of PHEOs/PGLs into cluster 1 and 2 provides us with additional knowledge related to the pathogenesis of these tumors, including the introduction of new treatment options for patients with metastatic PHEOs/PGLs. New discoveries related to the role of the *HIF-1/HIF-2 α* genes in the pathogenesis of almost all inherited PHEOs/PGLs may call for a new regrouping of these tumors and discoveries of new treatment targets.

Keywords

gene; mutation; paraganglioma; pheochromocytoma; succinate dehydrogenase

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Pheochromocytomas and paragangliomas (PHEOs/PGLs) are rare neuroendocrine tumors that produce catecholamines [1]. PHEOs/PGLs arise from three distinct parts of the neural crest: the adrenal medulla (PHEOs) and the sympathetic and parasympathetic paraganglia (PGLs) [2]. Initially, the pioneering work of Neumann *et al.* [3] showed that about one-quarter of these tumors were hereditary. According to the recent publications, up to 30–40% of these tumors are genetically inherited [3,4,5,6]. Now, the group of susceptibility genes includes the following genes: the von Hippel–Lindau (*VHL*) tumor suppressor gene, the rearranged during transfection (*RET*) protooncogene, the neurofibromatosis type 1 (*NF1*) tumor suppressor gene, genes encoding the four subunits (A, B, C, and D) of the succinate dehydrogenase (*SDH*) complex, and a gene encoding the enzyme responsible for flavination of the SDHA subunit (*SDHAF2*). In addition to these PHEO/PGL susceptibility genes, two other genes, KIF1B β and PHD2, have also been associated with PHEO/PGL development, although very rarely. Recently, three other genes, *TMEM127*, MYC-associated factor X (*MAX*), and hypoxia-inducible factor 2 α (*HIF2A*) (both somatic and germline mutations found), have been described [7,8,9,10,11,12]. Somatic mutations in the known PHEO/PGL susceptibility genes have been reported as an extremely rare event, but recently, Burnichon *et al.* [13] detected somatic mutations of the *RET* and *VHL* genes in about 14% of sporadic PHEOs/PGLs. Also, Welander *et al.* [14] suggest that the *NF1* gene constitutes the most frequent (24%) target of somatic mutations so far known in sporadic PHEOs. Furthermore, somatic mutations in *MAX* were found in 1.65% of tumors [15]. Thus, the proportion of all patients with PHEOs/PGLs because of the gene mutations described above is estimated to be approximately 50% at present (Table 1). In the present article, we focused on the role of new genes linked to the pathogenesis of PHEOs/PGLs and on clustering hereditary PHEOs/PGLs based on their transcriptional profile as described previously [13]. Discoveries of new genes and specific transcriptional profiles for PHEOs/PGLs will further provide new treatment strategies for these tumors.

TMEM127 MUTATION

Recently, Qin *et al.* [8] reported heterozygous germline mutations in the *TMEM127* gene in seven patients affected by PHEO. The *TMEM127* gene, located on chromosome 2q11, encodes a transmembrane protein of 238 amino acids. *TMEM127* is a highly conserved and broadly expressed protein with three transmembrane regions, but has no known functional domains. The *TMEM127* protein associates dynamically with the endosomes and may participate in the protein trafficking between the plasma membrane, the Golgi, and lysosomes [8]. Tumors with *TMEM127* mutations have a transcription signature comparable to that of *RET*-mutated and *NF1*-mutated PHEOs. However, neither RAS activation nor AKT phosphorylation was seen, indicating that *TMEM127* loss is not identical to either *NF1* or *RET* [8]. *In vitro* and in primary tumors, it was found that *TMEM127* functions as a negative regulator of the mammalian target of rapamycin (mTOR), or more specifically of mTORC1, but the mechanisms underlying this interaction have not yet been established. However, *TMEM127* knockdown, leading to an increase in the phosphorylation of mTORC1 targets, results in larger cells with higher rates of proliferation and hyperphosphorylation of mTOR effector proteins [8]. Thus, *TMEM127* is a new tumor-suppressor gene involved in

hereditary PHEOs/PGLs. *TMEM127* missense, frame shift, and nonsense mutations were detected in all three coding exons of the gene, but no large *TMEM127* deletions or duplications were found. Genetic studies of PHEO/PGL patients indicate a low prevalence of *TMEM127* mutations (~2% of all cases negative for other PHEO/PGL susceptibility mutations) [8,17■,18]. A unique finding in these patients was the older average age (42 years) at presentation, which is similar to sporadic cases, but older than that of carriers of mutations in other susceptibility genes [8,17■,18]. In most cases, *TMEM127* mutation carriers suffered from PHEOs only (unilateral as well as bilateral tumors) and secreted a high level of metanephrines. Only two mutations have been reported in a few patients with PGLs [19], one associated with multiple PHEO and retroperitoneal PGL and the other with bilateral carotid PGLs [8,17■,18,20]. Malignancy has been reported rarely [8,17■,18].

MAX MUTATION

In 2011, Comino-Mendez *et al.* [7■] identified *MAX* as a new PHEO tumor-suppressor gene in three independent patients with familial antecedents of the disease. The protein encoded by the *MAX* gene is a member of the basic helix–loop–helix leucine zipper (bHLHZ) family of transcription factors. The *MAX* protein is a ubiquitous, constitutively expressed protein that plays a central role in controlling the MYC/MAX/MXD1 (MAX dimerization protein 1) axis. MYC activates transcription binding to E-box DNA recognition sequences in target gene promoters through heterodimerization with MAX; heterodimers of MAX with MXD1 antagonize MYC-dependent cell transformation by transcriptional repression of the same E-box target DNA sequences [21,22]. *MAX* mutations are associated with bilateral PHEOs and an apparent paternal transmission of the disease [7■]. In a large international study, Burnichon *et al.* [15] confirmed that *MAX* germline mutations are responsible for PHEOs and PGLs in 1.12% of cases. In this study, patients with pathogenic *MAX* mutations had adrenal tumors, including 13 with bilateral or multiple PHEOs within the same adrenal gland. *MAX*-related thoracoabdominal PGLs were also found in the same study [15]. Thirty-seven percent of these patients had familial antecedents. Malignant disease developed in about 10.5% of patients [15]. However, Comino-Mendez *et al.* [7■] found metastasis at diagnosis in three out of eight probands. Therefore, mutations of *MAX* can be associated with a high risk of malignancy. Furthermore, somatic mutations in *MAX* were found in 1.65% of tumors [15]. The mutations were found in all five exons of the *MAX* gene, but were especially frequent in exons 3 and 4, corresponding to some of the most important residues within the conserved bHLH–Zip domain of MAX. The majority of the mutations led to the presence of truncated proteins, which resulted in the absence of the protein, as determined by immunohistochemistry [15]. How *MAX* mutations contribute to the pathogenesis of PHEO/PGL remains unclear. However, the ability of MYC to function independently of MAX has been demonstrated [23]. Therefore, Cascón and Robledo [21] suggested that the pivotal role of MAX in the MYC/MAX/MXD1 network is related more to the repression rather than to the activation of the MYC network.

HIF2A MUTATION

Zhuang *et al.* [9■] identified novel somatic mutations in the gene encoding HIF-2 α in multiple PGLs and duodenal somatostatinomas associated with polycythemia, suggesting

the existence of a new syndrome. Also, Favier *et al.* [24] found somatic HIF2A mutations that may lead to the pathogenesis of PHEO in a female patient. The existence of a new syndrome (potentially to be named Pacak–Zhuang syndrome) was then confirmed in a larger series of female patients [16■]. These patients were found to have polycythemia either at birth or in childhood together with multiple PGLs and somatostatinomas. Subsequently, Lorenzo *et al.* [12■] reported a novel *HIF2A* germline mutation in a patient with congenital polycythemia with multiple PGLs.

HIFs are transcription factors controlling energy, iron metabolism, erythropoiesis, development, glycolysis, and other cell functions [25,26■]. The HIF- β subunit is constitutively expressed, whereas the α subunits are inducible by hypoxia [27]. When these proteins are dysregulated, they often contribute to tumorigenesis and cancer progression [28,29]. However, mutations in the genes encoding HIFs have not previously been identified in any cancer. Dominantly inherited gain-of-function mutations of *HIF2A* were previously found to be associated with an increase of erythropoietin and congenital polycythemia [30,31]. In HIF-2 α -related polycythemia with or without PGLs, these mutations have been found mainly at hot spots in exon 12 [9■,30,31]. HIF-2 α gene mutations were found to disrupt prolyl hydroxylation of HIF-2 α and, in turn, recognition by the VHL protein, resulting in a failure of HIF-2 α ubiquitylation and its degradation. Thus, the longer half-life of the mutant HIF-2 α protein resulted in the upregulation of downstream HIF-2 α targets (EDN1, EPO, GLUT1, and VEGF), which is currently believed to be the pathogenic mechanism that leads to tumor development [9■]. Very recently, we have also identified a somatic HIF2A gene mutation in a patient with multiple PHEOs associated with polycythemia (unpublished observation).

THE CLUSTERS OF HEREDITARY PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS BASED ON TRANSCRIPTIONAL PROFILE

Hereditary and sporadic PHEOs/PGLs can be divided into two groups based on the transcription profile revealed by the genome-wide expression microarray analysis. The first group (cluster 1) includes tumors carrying *VHL* and *SDHx* (*SDHD*, *SDHB*, *SDHC*, *SDHA*, and *SDHAF2*) mutations and also accounts for about 30% of sporadic tumors [13,32,33]. The second group (cluster 2) represents the tumors carrying *NF1*, *RET*, and *KIF1B mutations, and also includes about 70% of sporadic tumors [5■,13,34■,35■]. The new *TMEM127* and *MAX* genes are most likely associated with cluster 2 and *HIF2A* with cluster 1 [9■,12■,13,15].*

Cluster 1

VHL/SDHx mutations lead to impaired degradation and accumulation of HIF-1/HIF-2 α and display signatures of pseudohypoxia, angiogenesis, increased reactive oxygen species (ROS), and reduced oxidative response, resulting in changes in the cell metabolism (energy metabolism regulation). HIF- α heterodimerizes with HIF- β and acts as an active transcription factor. Succinate that accumulates in the mitochondrial matrix owing to SDH dysfunction leaks out into the cytosol, where it inhibits the activity of HIF-1/HIF-2 α prolyl hydroxylase enzymes (PHDs – PHD1, PHD2, and PHD3, also known as EglN2, EglN1, and

Egln3, respectively) that hydroxylate two prolyl residues [36]. Hydroxylated HIF- α is recognized by the VHL protein and marked for degradation in the proteasome. If the *VHL* gene is mutated, the protein is not formed, so HIF- α cannot be degraded and therefore accumulates. Burnichon *et al.* [13] showed that *SDHx*-related and *VHL*-related PHEOs/PGLs shared overexpression of several genes involved in angiogenesis and the hypoxic pathway. Some genes were specifically overexpressed in *SDHx*-related tumors. These genes are involved in transcription regulation, protein transport, proliferation, energy metabolism, and cell adhesion. Also, several specifically overexpressed genes have been found in *VHL*-related tumors. These genes are *EGLN3* and *KISS1R*, as well as genes involved in glycolysis [13]. Burnichon *et al.* [13] found, which was also confirmed by Lopez-Jimenez *et al.* [33], that although *VHL/SDHx*-related tumors are associated with pseudo-hypoxia, some HIF target genes were differentially expressed between *SDHx* and *VHL*-related tumors. Most of these genes, such as *ENO1*, *BNIP3*, or *CA9*, are considered to be HIF-1 α -specific targets and were specifically induced in *VHL*-related tumors [13]. Therefore, these tumors were further divided into cluster 1A (*SDHx*) and cluster 1B (*VHL*).

The *SDHB* mutation is associated with malignancy and poor prognosis [37]. Burnichon *et al.* [13] found genes specifically overexpressed in *SDHB*-related PHEOs/PGLs, including MMP24, DSP, SIX1, LGR5, LAPT4B, and β -catenin, most of which are important in the development of metastasis.

Cluster 2

Cluster-2-related PHEOs/PGLs are linked together by the activation of kinase signaling pathways driven by the oncogenes that involve translation, initiation, and protein synthesis, and genes involved in neural/neuroendocrine identity [13,32, 35,38–40]. The proto-oncogene *RET* is a tyrosine kinase receptor primarily expressed in the neural crest cells. *RET* mutations have been associated with increased activation of PI3K/v-Akt signals [41]. *NF1* encodes for the protein neurofibromin, a GTPase-activating protein in the RAS signaling cascade and mTOR signaling pathway [42,43]. Thus, *RET* and *NF1* mutations lead to activation of the PI3K/AKT/ mTOR and RAS/RAF/MAPK signaling pathways. *TMEM127* mutations enhance mTOR activity independent of the *RET* and *NF1* pathways. Finally, *MAX* gene mutations result in the dysregulation of the MYC–MAX–MXD1 network connected with mTOR pathway function [15].

FUTURE TREATMENT

Whereas the most optimal treatment for benign PHEOs/PGLs is surgical resection, therapy for malignant/metastatic disease is unsatisfying at best. Understanding the specific genetic alterations of various PHEOs/PGLs will undoubtedly open promising new options for targeted therapies in the near future. Also, clustering PHEOs/PGLs by expression alterations can lead us to choose certain treatment targets. Thus, expression microarrays can be a more powerful tool for the detection of target genes and associated pathways involved in PHEOs/PGLs in the future [13,15,24,28,42,43].

Yang *et al.* [44] have recently demonstrated that the loss of *SDHB* function was because of a reduction in the mutant protein half-life by rapid proteasome degradation. The authors

found that histone deacetylase inhibitors (HDACi) stabilized the half-life of mutated SDHB proteins and their activity. Direct activation of PHD by the activator KRH102053 increases HIF-1/HIF-2 α hydroxylation and promotes its degradation [45,46].

Metastatic SDHx-related PHEO/PGL overexpresses heat shock protein 90 (HSP90), a molecular chaperone that assists in binding to HIF-1/HIF-2 α and promotes its stability by preventing ubiquitination and proteasomal degradation of HIF-1/HIF-2 α [25,47,48]. Thus, the inhibitors of HSP90, such as geldanamycin and analogs 17-allylaminogeldanamycin (17-AAG; tanespimycin) and 17-dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG; alvespimycin) or other new ones, are promising novel anticancer therapeutic agents [49,50]. Small-molecule inhibitors of glucose transporter 1 (GLUT1), such as WZB117 or STF-31, downregulate glycolysis and inhibit cancer cell growth *in vitro* and *in vivo* [51,52]. Favier *et al.* [53] showed that cluster 1 tumors display angiogenic markers such as vascular epithelial growth factor (VEGF), its receptors, HIF-2 α , angiopoietin-2, and the endothelin receptors ETA and ETB. Thus, these results suggest that there is a rationale for antiangiogenic therapy, including targeting the VEGF pathway using either humanized monoclonal anti-VEGF antibodies (Bevacizumab) or small tyrosine kinase inhibitors such as sunitinib or sorafenib [53]. Also, targeting HIF-1/HIF-2 α by HIF-1 α inhibitors (direct inhibitor PX-478 and indirect inhibitor PX-12) has shown antitumoral activity in human tumor xenografts in mice and also seems to be promising for malignant PHEO/PGL [54–56].

Favier *et al.* [53] showed that the mTOR pathway was potentially activated in half of PHEOs/PGLs. Nolting *et al.* [57] showed that the combination treatment with dual NVP-BEZ235 (PI3K/mTORC1 inhibitor) and lovastatin (inhibitor of ERK signaling) had a significant additive effect in mouse PHEO cells and resulted in inhibition of both AKT and mTORC1/p70S6K signaling without ERK upregulation.

The new therapeutic options outlined above are expected to be introduced in the near future.

CONCLUSION

In the near future, next-generation sequencing technology is predicted to replace conventional sequencing methods and a stepwise procedure for genetic screening will likely no longer be required. Similarly, whole-genome sequencing will allow the discovery of newer PHEO/PGL susceptibility genes. Molecular targeted therapies will appear as the most promising strategies for the management of patients with metastatic PHEO/PGL.

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KEY POINTS

- *TMEM127*, *MAX*, and *HIF2A* are the new susceptibility genes for PHEOs/PGLs.
- New syndromes (such as Carney–Stratakis syndrome, comprised PGL and GIST, and a new syndrome potentially to be named Pacak–Zhuang syndrome, comprised multiple PGLs and duodenal somatostatinomas associated with polycythemia in women) have been introduced.
- Genome-wide studies led to the identification of somatic mutations in about 14% of sporadic PHEOs/PGLs.
- Hereditary and sporadic PHEOs/PGLs are currently divided into two groups (SDHx/VHL and RET/NF1) based on the transcription profile revealed by genome-wide expression microarray analysis or by other approaches.
- Deep knowledge of the genetic changes and expression profiles will introduce new targeted therapy for malignant PHEOs/PGLs.

Table 1

Genotype-phenotype correlations in pheochromocytoma/paragangliomas because of mutations in susceptibility genes

Gene	Locus	Syndrome	Inh.	Malignant PHEO/PGL	Single PHEO	Bilateral PHEO	TAPGL	HNPGL	Multiple PGLs	Biochemical phenotype
<i>SDHA</i>	5p15		AD	?	–	–	+	+	–	?
<i>SDHB</i>	1p36.13	PGL4	AD	+++	++	+	+++	++	++	MT, NMN, MTY or NS
<i>SDHC</i>	1q21	PGL3	AD	±	±	–	+	++	+	MT, NMN or NS
<i>SDHD</i>	11q23	PGL1	AD PI	+	+	+	++	+++	+++	MT, NMN, MTY or NS
<i>SDHAF2</i>	11q13.1	PGL2	AD PI	?	–	–	–	+++	++	?
<i>VHL</i>	3p25–p26	VHL	AD	+	++	+++	+	±	+	NMN
<i>NFI</i>	17q11.2	NF1	AD	+	+	±	–	–	–	MN, NMM
<i>RET</i>	10q11.2	MEN	AD	±	++	++	–	–	–	MN, NMM
<i>MAX</i>	14q23.3		AD PI	+	++	++	–	–	–	Mixed: NMN + MN
<i>TMEM127</i>	2q11.2		AD	±	+++	++	±	±	±	MN
<i>HIF2A</i>	2p21–p16		Somatic ^a	?	±	^b	++	–	++	NMN

AD, autosomal dominant; HNPGL, head and neck paraganglioma; Inh, inheritance; MN, metanephric; MTY, methoxytyramine; NMN, normetanephine; NS, nonsecreting; PGL, paraganglioma; PHEO, pheochromocytoma; PI, paternal inheritance; TAPGL, thoracic or abdominal paraganglioma; ?, unknown. *SDHA*-related paragangliomas can be also associated with *SDH*-deficient gastrointestinal stromal tumors (GISTs). This autosomal-dominant familial paraganglioma and GIST syndrome is known as Carney–Stratakis syndrome [11]. Recently, Pacak–Zhuang syndrome including paraganglioma, somatostatinoma, and polycythemia in women has been introduced. This syndrome is associated with somatic *HIF2A* gain-of-function mutation [16].

^a Rarely germline.

^b Taieb, Pacak, unpublished observation.