Chapter

Pheochromocytomas and Paragangliomas: Genotype-Phenotype Correlations

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Abstract

Pheochromocytomas and paragangliomas are rare neuroendocrine tumors, with genetic background in about 40% of cases, involving more than 30 susceptibility genes. The susceptibility genes can be divided into three main molecular clusters: pseudohypoxic, kinase signaling, and Wnt signaling. Biochemical characterization of these particular tumors should be integrated into the diagnostic algorithm because it can help apply personalized medicine principles and targeted therapy. These tumors can present with very different genotype-phenotype correlations, and their characterization can help the clinical practitioner make optimal clinical management decisions and prioritize genetic testing. This chapter summarizes the most important aspects of genetics and clinical characteristics, together with new genotype-phenotype correlation data.

Keywords: pheochromocytomas, paragangliomas, genotype-phenotype correlations

1. Introduction

Pheochromocytomas (Pheos) and paragangliomas (Pgls) are chromaffin cell-derived tumors that can develop from the adrenal medulla or the extra-adrenal paraganglia. There are two types of Pgls: sympathetic and parasympathetic. Both Pheos and sympathetic Pgls are catecholamine-producing tumors. Frequently parasympathetic Pgls are located in the head and neck region, they do not have chromaffin cell phenotypic features, and they are in a vast majority of non-secreting tumors [1, 2].

Pheos are rare tumors, with an annual incidence of 2 to 9.1 per 1 million for adults patients [3].

The prevalence of Pheos and Pgls in patients with hypertension is between 0.2 and 0.6% [4].

The early detection of Pheos/Pgls is mandatory because if they go undiagnosed and untreated, the cardiovascular morbidity and mortality rates are high. Furthermore, the risk of metastatic disease (the presence of metastases in nonchromaffin tissue) is increased between 10 and 20% [5, 6].

In the last two decades and especially in the last seven years of medical researches, clinical medical studies showed that 40% of these tumors are associated with underlying germline or somatic mutations in about 30 susceptibility genes. Next-Generation Sequencing (NGS) technology has made the sequencing of the whole exome routinely available, and many clinical research papers reported specific genes associated with Pheos and Pgls [2].

Catecholamines are produced within chromaffin cells, and their derivatives are metabolized within the same cells by an enzyme called catechol-O-methyltransferase. Norepinephrine and epinephrine are metabolized to normetanephrine and metanephrine. Also, dopamine is metabolized to 3-methoxytyramine [7].

Depending on biochemical secretory characteristics, Pheos and sympathetic Pgls can be divided into three different biochemical or secretory phenotypes. Pheos and sympathetic Pgls with the noradrenergic phenotype secrete especially norepinephrine. Besides, Pheos and sympathetic Pgls with the adrenergic phenotype produce epinephrine predominantly. Supplementary, Pheos, and sympathetic Pgls, which secrete dopamine, are categorized into a third category named the dopaminergic phenotype [8].

Congruent to The Endocrine Society Clinical Practice Guidelines [4], the clinical evaluation of Pheos or Pgls should start with measurements of plasmatic free metanephrines preferentially carried out using blood samples collected in the supine position or urinary fractionated metanephrines, altogether with urinary creatinine determination. Also, in suspicious dopamine secreting tumors, the plasmatic dosage of 3-methoxytyramine is indicated [7].

If the initial biochemical evaluation indicates elevated 3-fold or more above the upper cutoffs of catecholamines, the next clinical step should be imaging studies to localize the tumor. The preferred initial imaging method is computed tomography, followed by magnetic resonance imaging to detect metastatic disease, and 123I-metaiodobenzylguanidine (MIBG) scintigraphy is recommended [4].

Catecholamine hypersecretion syndrome can induce numerous lethal conditions due to the high impact on the cardiovascular system, potentially causing sudden deaths. Clinical consequences of catecholamine excess can be myocardial infarction, cardiac arrhythmias, severe acute hypertension, pulmonary edema, heart failure, hypertensive encephalopathy, and cardiogenic shock [9, 10].

In addition to catecholamines' secretion, Pheos and Pgls could also secrete a wide diversity of biomarkers, such as chromogranin A, which can monitor disease progression [11, 12]. Subsequently, chromogranin A is released by exocytosis from the storage granules and catecholamines into the bloodstream to sympathetic or adrenal stimulation. Therefore, chromogranin A level corresponds to the norepinephrine and epinephrine serum levels in the context of Pheos/Pgls [12].

Moreover, chromogranin A levels were reported to be proportional to the tumor mass, metastatic disease, especially liver disease, and the presence of the SDHB gene mutation [13].

Furthermore, Pheos and Pgls could be responsible in rare situations of ectopic secretion syndromes, with mostly cited cases of ectopic ACTH secretion syndrome, PTH/PTHrp, and interleukin 6 secretion [14]. However, the majority of ectopic secretion is encountered in non-metastatic tumors.

These particular tumors can present with very different genotype-phenotype correlations. Depending on the affected gene and its activated intracellular signaling pathways, each tumor is clinically different.

The genetic involvements, together with the good predictive value of histological PASS -Pheochromocytoma of the Adrenal Gland Scaled Score and GAPP algorithms, provide novel prognostic biomarkers and new therapeutic approaches for Pheos and Pgls [15].

2. Genetic background

More than 30 genes are currently associated with hereditary Pheos and Pgls, leading to genetic cause in about 40% of these tumors. Given this high frequency of genetic mutations, all patients with Pheos and Pgls should undergo genetic testing [16].

Genetic screening should be done mostly in patients with a positive family history, young age at diagnosis, bilateral adrenal Pheos, and metastatic or multifocal Pheos/Pgls [4].

NGS technique of targeted gene panels is now the recommended genetic screening method in all patients diagnosed with Pheos/Pgls [17].

Depending on the main signaling transduction pathways, these genes have been grouped into three clusters: pseudohypoxemia, the tyrosine kinase, and the WNT pathways [18].

Gene clusters have different molecular routes to tumorigenesis and provide a specific substrate to explore. Furthermore, each cluster is associated with particular clinical characteristics and with a specific phenotype.

2.1 Pseudohypoxic cluster

The pseudohypoxic pathway involves the Krebs cycle modulation. It is characterized by mutations in genes encoding the endothelial pas domain protein 1/hypoxia-inducible factor type 2A (EPAS1/HIF2A), von Hippel-Lindau tumor suppressor (VHL), succinate dehydrogenase subunits SDHx (SDHA, SDHB, SDHC, SDHD), succinate dehydrogenase complex assembly factor 2 (SDHAF2), egl-9 prolyl hydroxylase 1 and 2 (EGLN1/2), fumarate hydratase (FH), malate dehydrogenase 2 (MDH2), prolyl hydroxylase types 1 and 2 (PHD1 and PHD2), and isocitrate dehydrogenase (IDH) [19, 20].

Furthermore, the hypoxia/pseudohypoxia cluster is divided into two subgroups. The first is associated with germline mutations that affect Krebs cycle and especially the succinate dehydrogenase subunits (SDHA, SDHB, SDHC, SDHD, and SDHAF2), the fumarate hydratase (FH), the malate dehydrogenase 2 (MDH2), and isocitrate dehydrogenase (IDH). The second subgroup involves mutation VHL/EPAS1 genes, with a high rate of angiogenesis and over-expression of vascular endothelial-vessel growth factor (VEGF), which increases neo-angiogenesis [3].

Tumors caused by these specific genetic mutations are pseudohypoxic. Hence the upregulation of HIF-α is not caused by hypoxia but by other molecular pathways. Mutations in genes encoding enzymes lead to the misregulation of cellular metabolism, chromatin remodeling, DNA methylation changes, and reactive oxygen species production. These specific genetic mutations can induce a metabolic alteration that results in an increased dependence on glycolysis, promotion of angiogenesis, and succinate, fumarate, and L-malate accumulation. Thus, these high concentrations of Krebs cycle metabolites lead to activation of the oncogenetic pathway [16, 21].

Furthermore, the hypoxia pathway activation in these types of tumors implicates the glycolytic shift, a typical biochemical feature of these tumors [3].

Tumors in this cluster are more clinically aggressive and are often diagnosed with metastatic disease. Also, multiple and multifocal tumors are persistent, and the prognostic of patients in this gene's cluster is most deficient than other susceptibility gene mutations. Moreover, almost all tumors associated with cluster 1 (except for VHL- gene) gene mutations are extra-adrenal, and they have the noradrenergic phenotype, secreting norepinephrine [22, 23].

2.2 Kinase signaling cluster

Dysregulation of the receptor kinase signaling pathway consists of germline or somatic mutations in the RET proto-oncogene (RET), neurofibromin 1 (NF1) tumor suppressor, H-RAS and K-RAS proto-oncogenes, transmembrane protein 127

(TMEM127), Myc-associated factor X (MAX), chromatin remodeler ATRX, and cold shock domain-containing E1 (CSDE1) [24, 25].

Patients with tumors caused by gene mutations in this cluster have an excellent general prognosis, except for those with ATRX mutations, where recurrence and metastatic disease are more common [26].

Furthermore, Pheos and Pgls from this cluster have a more differentiated cellular adrenergic phenotype, they are mostly adrenal tumors, and they rarely develop secondary lesions, except for those with ATRX gene mutations [16].

2.3 Wnt signaling cluster

The Wnt pathway plays an essential role in the development, organogenesis and is vital for cell survival, migration, and chemotaxis. The Wnt signaling pathway is demodulated in different diseases such as cancer, bone diseases, cardiovascular diseases, hereditary colorectal cancer, intellectual disability syndrome, neuropsychiatric diseases [3, 27].

Tumors overexpressing genes of the Wnt and Hedgehog pathways consist of the Wnt-altered subgroup. These tumors are related to somatic mutations in CSDE1 and the mastermind, like transcriptional coactivator 3 (MAML3) [27].

These genotypes display mixed characteristics regarding catecholamine secretion phenotype, involving both noradrenergic and adrenergic phenotype. Moreover, Wnt pathway genes are associated with tumors with a high frequency of metastatic or recurrent disease [28, 29].

Furthermore, Wnt-altered tumors exhibit high expression of CHGA, a gene that encodes chromogranin A, inducing high levels of this biomarker, useful for diagnosing and monitoring disease progression [16, 21].

Moreover, somatic mutations in the TERT promoter (SDHx-deficient PPGL) and the chromatin modifier KMT2D have also been identified, but they remain validated by future researches [23]. However, the somatic mutations in genes associated with telomere preservation (inactivation of the ATRX gene or transcriptional activation of TERT) are associated with tumors with more aggressive clinical features [23].

3. Biochemical diagnosis and specific secretory phenotypes

Patients with Pheos can present with a complex spectrum of nonspecific symptoms, making it challenging for clinical physicians to diagnose correctly.

The biochemical phenotype of the tumor influences the clinical presentation. These tumors' hormonal phenotypes have systemic effects, especially on the cardiovascular system and gastrointestinal, ocular, renal systems.

Most patients present with typical clinical signs and symptoms of catecholamine excess, including sustained or paroxysmal hypertension episodes, sweating, headache, and palpitations. Symptoms may be precipitated due to external factors, including a tyramine-rich diet, specific drugs such as histamine, tricyclic antidepressants, monoamine oxidase inhibitors, and anesthesia [30, 31]. Moreover, in 10 to 20% of cases, patients may be entirely asymptomatic, with Pheos/Pgls diagnosed as incidentalomas on imaging studies [15].

These clinical characteristics can be grouped into three distinct biochemical phenotypes: noradrenergic, adrenergic, and dopaminergic, defined by elevations in epinephrine, norepinephrine, and dopamine [23].

Besides, there is a rare subset of Pgls, which are non-secreting tumors, and they are referred to as biochemically silent, although elevated levels of chromogranin A or specific neuronal enolase can be detected [12].

Studies reported that tumors with the adrenergic phenotype are more differentiated than the noradrenergic phenotype, which may be more differentiated than the dopaminergic phenotype, influencing catecholamine secretion levels [6].

Numerous reports showed a positive correlation between tumor dimensions and plasma and urinary concentrations of metanephrines. Moreover, patients with metastatic disease have high levels of metanephrines corresponding to the tumor burden. Also, chromogranin A levels were associated with tumor mass and metastatic disease, especially with secondary liver determinations [11, 13].

3.1 The noradrenergic phenotype

The noradrenergic phenotype consists of tumors producing norepinephrine as the main secretion pattern. The measurement of plasmatic free normetanephrine clinically diagnoses this phenotype. In most cases, these types of tumors are localized in extra-adrenal regions, but some medical reports describe them within the adrenal glands [23].

Tumors secreting predominantly norepinephrine are associated with a lack of signs and symptoms related to catecholamine excess syndrome, and they are more frequently clinically silent. Patients can have sustained hypertension due to norepinephrine's physiological action on the α1 receptors, inducing vasoconstriction. Also, the noradrenergic phenotype can have greater intra-operative hemodynamic instability compared with patients with adrenergic phenotype [23]. Furthermore, α receptor blockage in these patients is the first line of therapy for pre-operative patients' management [32, 33].

Additionally, norepinephrine's vasoconstrictor effect can cause vasospasms of the cerebral, ocular, gastrointestinal, and renal circulation leading to an ischemic episode or stroke, optic neuropathy, intestinal necrosis or ischemia, and renal artery stenosis, respectively. Moreover, norepinephrine cause reduced intestinal motility, leading to constipation, paralytic, ileus, and intestinal pseudo-obstruction. Furthermore, intestinal circulation vasospasms can also lead to decreased intestinal motility with bowel ischemia and gastrointestinal bleeding, increasing the risk of developing colonic perforation and abdominal sepsis [34, 35].

Noradrenergic phenotype is suggestive of mutations in cluster 1 category or the pseudohypoxic pathway, consisting of the next following genes: succinate dehydrogenase subunits SDHx (SDHA, SDHB, SDHC, SDHD), succinate dehydrogenase complex assembly factor 2 (SDHAF2), von Hippel-Lindau tumor suppressor (VHL), egl-9 prolyl hydroxylase 1 and 2 (EGLN1/2), malate dehydrogenase 2 (MDH2), endothelial pas domain protein 1/hypoxia-inducible factor type 2A (EPAS1/HIF2A), fumarate hydratase (FH), and isocitrate dehydrogenase (IDH) [6, 25].

3.2 The adrenergic phenotype

Tumors classified as the adrenergic phenotype are characterized by increased production and secretion of epinephrine. Epinephrine has numerous physiological systemic effects, and it primarily stimulates only β1 and β2 receptors [10].

Patients with Pheos and sympathetic Pgls secreting epinephrine have more frequently paroxysmal symptoms of hypertension, palpitations, headache, flushing, and sweating because of their effect on hemodynamics and metabolism [36]. Moreover, the adrenergic phenotype catecholamines can be associated with a decline in the left ventricular systolic function due to the catecholamine-induced myocarditis, also called pheochromocytoma-associated catecholamine cardiomyopathy [37, 38].

These types of tumors are also well-differentiated, and they are frequently localized within the adrenal gland. Initially, it was presumed that the increased expression of the Phenylethanolamine N-methyltransferase (PNMT) gene is involved in the pathophysiology of adrenergic phenotype, but further studies stated that the presence of glucocorticoids is not ample enough to induce the adrenergic phenotype [20].

Furthermore, adrenergic phenotype tumors are frequently associated with adrenal diabetes and dyslipidemia, caused by epinephrine's metabolic effects [39].

Mutations specific to adrenergic phenotype are grouped into cluster 2, causing activation of kinase signaling pathways. The genes included in cluster 2 are RET proto-oncogene (RET) involved in the development of MEN2 syndrome, neurofibromin 1 (NF1) tumor suppressor gene involved in neurofibromatosis type 1, H-RAS and K-RAS proto-oncogenes, transmembrane protein 127 (TMEM127), chromatin remodeler (ATRX), Myc-associated factor X (MAX), and cold shock domain-containing E1 gene (CSDE1) [31].

Patients presenting with predominantly elevated metanephrines should undergo genetic screening for RET and NF1 mutations for the first genetic approach.

All the patients should have pre-operative preparation with α-blockers or other medications to control hypertension, arrhythmia, and volume expansion [3].

3.3 The dopaminergic phenotype

The dopaminergic phenotype consists of a sporadic group of neuroendocrine tumors that produce and secrete dopamine and its metabolite, 3-methoxytyramine.

Urinary dopamine levels are unreliable markers of this phenotype. Therefore the dopaminergic phenotype can be evaluated by plasmatic determination of dopamine and 3-methoxytyramine levels [7, 40].

However, Pheos and Pgls associated with SDHx mutations can produce and/or secrete dopamine and 3-methoxytyramine.

Tumors of this subgroup are frequently found in extra-adrenal sites and may be malignant. Mainly, carotid body tumors, a specific type of head and neck Pgls, produce dopamine, which is continuously metabolized into its metabolite [41].

Regarding dopamine's physiological roles, it is well known that it acts will on D1 and D2 dopaminergic receptors.

Activation of D1 receptors, located on vascular smooth muscle cells, may lead to arterial renal vasodilatation and stimulation of the gastrointestinal tract. Therefore, studies reported case reports with patients with chronic diarrhea, nausea, vomiting, abdominal pain, weight loss [42].

In contrast, D2 receptors, located in the central nervous system, inhibit norepinephrine secretion, and have a mild negative inotropic effect on the cardiovascular system. This mechanism offers a possible explanation for the absence of hypertension and palpitations in patients with dopaminergic phenotypes [10]. Also, patients can have nausea, emesis, and hypotension.

Furthermore, 3-methoxytyramine, the O-methylated dopamine metabolite, is a biomarker useful for diagnosing extra-adrenal tumors and multifocal disease [7]. Moreover, increased levels are specific to patients with SDHB and SDHD mutations and a highly suggestive risk of malignancy [43].

The main characteristics for these tumors and genotype-phenotype correlations are summarized in **Table 1**.

The leading cause of death in patients with Pheos and Pgls is a metastatic disease that can occur in about 10–20% of cases [44, 45]. The most cited prognostic factors associated with metastasis are extra-adrenal location, a large dimension of

Biochemical phenotype	Hormones	Genetics	Risk of malignancy
Adrenergic	Epinephrine	Cluster 2 category/kinase signaling pathway	Increased risk of malignancy in ATRX gene mutations
Noradrenergic	Norepinephrine	Cluster 1 category/ pseudohypoxic pathway	Increased risk of malignancy in SDHB and SDHD gene mutations
Dopaminergic	Dopamine and 3-methoxytyramine	SDHB and SDHD mutations	Increased risk of malignancy

Table 1.
Genotype-phenotype correlations.

the primary tumor germline SDHB mutations, ATRX mutation, and catecholamine secretion (noradrenergic or dopaminergic) [6, 16, 46].

4. Peculiarities of pediatric pheochromocytoma

The subgroup of pediatric Pheos and Pgls is still poorly studied, but the latest data stated that they have peculiarities compared to the adult population.

Pediatric Pheos and Pgls have a prevalence of 8–9% in recent studies [47], with a median age between 12 and 14 years, the youngest age reported to date is four years, and a preponderance of boys between 52.7% to 65.5% [48].

In terms of diagnosing algorithms, The European practice guidelines recommend diagnosing Pheos/Pgls plasmatic metanephrines and normetanephrine, 24-hour urinary fractionated metanephrines, and optionally chromogranin A dosing [24].

In the study of [49], the authors reported a high incidence of 70% of genetic causes of Pheos/Pgls, with pathogenic mutation, detected preferably with the use of NGS.

Considering the clinical spectrum of pediatric Pheos, the prevalence of sustained hypertension is more common in children 70% than adults (50%) [50].

Furthermore, a large majority of 70–80% of pediatric catecholamine secreting tumors are functional, making the clinical diagnosis more approachable. Moreover, 10% of the tumors can be malignant, with about 20% found at multifocal sites [50–52]. Subsequently, an increased incidence of extra-adrenal tumors of about 30% was reported in recent studies [48, 49, 53].

In terms of the genetic landscape of pediatric Pheos, to date, ten genes have been described in the medical literature in association with Pheos at a pediatric age: RET, VHL, NF1, SDHD, SDHB, SDHA, FH, MAX, HIF2A, and PHD1 [24]. Thus, clinicians should always bear in mind the high frequency of the next implicated genes: VHL mutations as the most prevalent in pediatric patients ranging from 28.0% to 49.0% of cases, followed by SDHB and SDHD, RET mutations (1.0–5.4% of cases), and NF1 gene mutations (3.0% of cases) [24, 54].

Another important aspect is that about 50% of pediatric Pheos/Pgls can recur, compared with the 15–20% proportion reported in the adult population as a 10-year probability of recurrence [3]. Subsequently, in the pediatric population, a secondary tumor can be diagnosed by 30 years, underling the necessity of proper lifelong monitoring [49, 51].

5. Conclusions

New data on genetic, metabolic, and biochemical alterations of Pheos and Pgls allow us to look for genotype-phenotype correlations.

Depending on biochemical secretory characteristics, Pheos and Pgls can be divided into three different biochemical or secretory phenotypes: adrenergic, noradrenergic, and dopaminergic.

Depending on the affected gene and its activated intracellular signaling pathways, each tumor is clinically different.

Kinase signaling cluster genes are associated with tumors with an adrenergic phenotype consisting of epinephrine secretion. These tumors are mostly adrenal tumors, and they rarely develop metastatic disease, except for those associated with ATRX gene mutations.

Noradrenergic phenotype is suggestive of mutations in the pseudohypoxic pathway genes.

The dopaminergic phenotype consists of a sporadic group of neuroendocrine tumors that produce and secrete dopamine, and they are associated with SDHx mutations.

Regarding pediatric Pheos, the most affected genes are represented by VHL, followed by SDHB, SDHD, and NF1. Knowing the high incidence of germline mutations in the pediatric population, lifelong monitoring of secondary lesions is recommended.

All patients diagnosed with Pheos and Pgls should undergo genetic testing.

Genotype-biochemical phenotype correlations could help in genetic testing decision making.

Further studies are necessary for the complete identification of genotype-specific biochemical markers, which will be important in monitoring disease progression and determining treatment strategies. Furthermore, understanding of the metabolic and genetic basis of Pheos and Pgls will lead to the development of effective forms of therapy for these particular tumors.

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