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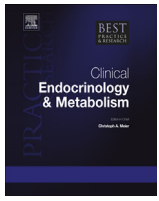

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An overview of 20 years of genetic studies in pheochromocytoma and paraganglioma

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Paragangliomas and pheochromocytomas (PPGL) are rare neuroendocrine tumours characterized by a strong genetic determinism. Over the past 20 years, evolution of PPGL genetics has revealed that around 40% of PPGL are genetically determined, secondary to a germline mutation in one of more than twenty susceptibility genes reported so far. More than half of the mutations occur in one of the *SDHx* genes (*SDHA, SDHB, SDHC, SDHD, SDHAF2*), which encode the different subunits and assembly protein of a mitochondrial enzyme, succinate dehydrogenase. These susceptibility genes predispose to early forms (*VHL, RET, SDHD, EPAS1, DLST*), syndromic (*RET, VHL, EPAS1, NF1, FH*), multiple (*SDHD, TMEM127, MAX, DLST, MDH2, GOT2*) or malignant (*SDHB, FH, SLC25A11*) PPGL. The discovery of a germline mutation in one of these genes changes the patient's follow-up and allows genetic screening of affected families and the presymptomatic follow-up of relatives carrying a mutation.

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Introduction

Paragangliomas (PGL) are rare endocrine tumours that develop at the expense of ortho- and parasympathetic systems. They can arise from the cervical region down to the pelvic area. PGL located in the adrenal medulla are called pheochromocytomas (PCC). These tumours may be diagnosed because of a compression syndrome (cranial nerves palsy in case of cervical PGL), or by a secreting syndrome. Indeed, paraganglioma and pheochromocytoma (PPGL) can produce catecholamines (dopamine, norepinephrine, and/or epinephrine) and be responsible for cardio- or cerebrovascular complications. Ten to 15% of PPGL are metastatic.

One of the great specificity of these tumours is their strong genetic determinism since it is now considered that PPGL is the most frequently heritable tumour with more than 20 susceptibility genes identified so far [1–7], for which germline mutations can be found in about 40% of cases. A meta-analysis performed by the Mayo Clinic has shown that about 12% of patients with an apparently sporadic PPGL (single benign PPGL without family context) actually carry a mutation in one susceptibility gene [8]. The knowledge of PPGL genetic determinism has rapidly increased over these last 20 years, erasing the previous dogma of that 10% of PPGL were inherited, mostly in syndromic forms. *RET*, *EPAS1, GOT2* and *DNMT3A* genes are oncogenes. Other predisposing genes are tumour suppressors, requiring the association of a germline mutation and a somatic loss of heterozygosity (LOH) or a second mutation on the other allele, according to Knudson's "two hits" model [9].

Because of this important genetic determinism, current guidelines do recommend genetic testing for all patients suffering from PPGL [10,11], in addition to hormonal measurements and imaging (radiological and nuclear medicine imaging). Indeed, knowledge of the genetic status is one of the key elements for an accurate diagnosis, follow-up and prognosis of affected patients [12]. Moreover, tumour and secretory phenotype are different according to genotype [13–16]. In this review we will describe the evolution of the genetics of PPGL with a main focus on genes implicated at the germline level (Table 1).

Table 1
Summary of phenotype of genetic PPGL.

Gene	Mutation frequency	Age at diagnosis	Main localization	Multiple PPGL	Malignant PPGL	Secreting phenotype
NF1	3%	40–50 yrs	PCC	20–40%	Rare	Norad + Adre
VHL	7%	20–30 yrs	PCC/APGL	40–60%	Rare	Norad
RET	6%	30–40 yrs	PCC	66%	Rare	Norad + Adre
EPAS1	1%	20–30 yrs	PCC/TAPPGL	50%	Rare	Norad, EPO
EGLN1	2 patients	NA	APGL	NA	Rare	Norad
SDHA	<5%	35–40 yrs	CPGL > APGL	<5%	Rare	Norad, Dopa, NS
SDHB	10%	30–40 yrs	APGL > CPGL	20%	40%	Norad, Dopa, NS
SDHC	1%	35–40 yrs	CPGL	30%	Rare	Norad, Dopa, NS
SDHD	9%	30–40 yrs	CPGL	66%	Rare	Norad, Dopa, NS
SDHAF2	<1%	30–40 yrs	CPGL	75%	Rare	NS
FH	1%	30–40 yrs	APGL	40%	60%	Norad, Dopa, NS
TMEM127	1–2%	35–40 yrs	PCC	15–66%	Rare	Norad + Adre
MAX	1%	35–40 yrs	PCC	50%	Rare	Norad
MDH2	5 patients	30–40 yrs	PCC/APGL	40%	40%	Norad, NS
GOT2	1 patient	NA	APGL	1 pts	1 pts	Norad
SLC25A11	8 patients	50–60 yrs	APGL	No	70%	Norad, NS
DLST	4 patients	20–30 yrs	TAPPGL	4 pts	rare	Norad
H3F3A	2 patients	20–30 yrs	APGL/PCC	½ pts	½ pts	NA
DNMT3A	2 patients	20–30 yrs	CTPGL	½ pts	rare	Norad
MET	1 family	NA	PCC	NA	NA	NA
MERTK	2 patients	NA	PH/APGL	½ pts	½ pts	NA
KIF1B	2 patients	NA	PCC	NA	NA	NA

Yrs: years, APGL: abdominal PGL, CPGL: cervical PGL, TAPPGL: thoracic, abdominal or pelvic PGL, NA: not available, Adre: adrenaline secretion, Norad: noradrenaline secretion, Norad + Adre: secretion of both adrenaline and noradrenaline, Dopa: Dopamine secretion, NS: non secreting.

"Old genes": syndromic forms of PPGL

At the end of the 90's, three different PPGL susceptibility genes (*NF1, RET* and *VHL)* corresponding to three different autosomal dominant syndromic diseases (neurofibromatosis type 1, multiple endocrine neoplasia type 2 and von Hippel Lindau disease, respectively) were known.

*Neurofibromatosis type 1 (*NF1 *gene)*

The *NF1* gene encodes neurofibromin and mutations in this gene are responsible for neurofibromatosis type 1 (NF1) or von Recklinghausen disease, an autosomal dominant pathology with high penetrance. Its prevalence is estimated at 1/3000 [17]. The diagnosis is based on the 7 NIH consensus criteria [18], and is made in 95% of cases on these clinical criteria from the age of 11 [19].

Patients with neurofibromatosis type 1 develop PPGL in 0.1–5.7% of cases, around the age of 40 [14,20]. In the vast majority of cases, these are epinephrine-secreting PCC, metastatic in 10% of cases and bilateral in 20–40% of cases. Interestingly, these PCC are found incidentally in 30% of cases, and less than 20% of patients have catecholaminergic symptoms [20]. Interestingly, a recent study reports *NF1* germline mutations in PPGL patients without clinical phenotype of Neurofibromatosis type 1, suggesting that *NF1* gene analysis should be performed in all PCC patients [21].

*von Hippel-Lindau disease (*VHL *gene)*

VHL germline mutations predispose to von Hippel-Lindau disease (VHL), an autosomal dominant syndrome which an incidence estimated at 1/36,000. Penetrance is almost complete at 65 years old [22]. This syndrome is characterized by the development, with variable expressivity of different tumours:

- clear cell renal cell carcinomas (ccRCC, 70% at age 60, [22]),
- PPGL (24% of patients),
- retinal and/or central nervous system hemangioblastomas (80% and 75% respectively),
- pancreatic neuroendocrine tumours (5–17% of patients) and/or cysts (80% of patients) [22],
- tumours of the endolymphatic sac (10–15% of patients) [23],
- epididymal or broad ligament cystadenomas.

Two phenotypes have been described in patients with *VHL* gene mutations, based on the risk of developing a PPGL: type 1 VHL disease, in which the PPGL risk's is low, and *VHL* mutations more frequently truncating, and type 2 VHL disease, associated with a high risk of developing a PPGL. Type 2 VHL is subdivided into 3 subgroups: type 2A where the risk of ccRCC is high, type 2B where the risk of kidney cancer is low, and type 2C where patients develop only PPGL. Mutations responsible for VHL type 2 are missense mutations.

Patients with a *VHL* gene mutation often develop PPGL before the age of 20, located in the adrenal medulla or the abdomen. These PPGL are often bilateral, either synchronous or metachronous (40–60% of cases). Family histories of VHL disease or syndromic lesions associated with PPGL are found in two-thirds of cases [14].

Interestingly, mutation in a *VHL* cryptic exon, located in the intron 1, was recently described in a large family with VHL disease. Cryptic *VHL* mutations alter the *VHL* mRNA splicing and lead to the under expression of VHL protein [24]. These cryptic exon mutations seem to be a rare event in PPGL patients [25].

*Multiple endocrine neoplasia type 2 (*RET *gene)*

The *RET* proto-oncogene encodes a tyrosine kinase receptor [26], and gain of function mutations are responsible for multiple endocrine neoplasia type 2 (MEN2), affecting 1/30,000 individuals. These mutations have an autosomal dominant transmission and cause self-activation of the RET receptor.

These mutations lead to three different clinical phenotypes with good genotype–phenotype correlations:

- MEN2A or Sipple syndrome (70%–80% of cases) is characterized by the occurrence of medullary thyroid carcinoma (MTC), PCC and hyperparathyroidism (HPTH). Some patients may also develop amyloid lichen.
- MEN2B or Gorlin syndrome (5% of cases) is characterized by the occurrence of MTC, PCC, mucosal neuromas, stomach or intestinal gangliomatosis, and a marfanoid habitus.
- Familial medullary thyroid carcinoma or Farndon's syndrome (10–20% of cases) is characterized by the isolated development of an MTC [27].

MEN2 prognosis is based on the MTC aggressiveness. Correlations between genotype and aggressiveness of MTC are well established. *RET* mutations were recently reclassified into 3 levels by the American Thyroid Association according to the aggressiveness of the MTC (Moderate, High, Highest) [28].

PCC are present in about 50% of patients with MEN2A or MEN2B and usually develop around the age of 30 [27]. Two-thirds of patients develop bilateral PCC [14,16].

The 2000s: the discovery of the major implication of the *SDHx* genes in PPGL tumourigenesis

SDHx genes (*SDHD, SDHC, SDHB, SDHA* and *SDHAF2*) account for almost half of the mutated cases at the germline level in PPGL [29,30]. The *SDHA, SDHB, SDHC* and *SDHD* genes encode the 4 subunits of succinate dehydrogenase (SDH) or mitochondrial complex II, an enzyme located in the mitochondria inner membrane. This enzyme is at the crossroads of two metabolic pathways. It oxidizes succinate to fumarate in the Krebs cycle, and is involved in the transfer of electrons in the mitochondrial respiratory chain.

SDHx genes are tumour suppressor genes. A germline mutation in one of these genes, associated with somatic LOH leads to a complete loss of SDH activity, responsible for succinate accumulation in the cytoplasm that will behave as an oncometabolite [31,32].

These mutations are transmitted in an autosomal dominant manner for *SDHA, SDHB*, and *SDHC* genes, and in an autosomal dominant manner associated with paternal transmission for *SDHD* and *SDHAF2*.

Different phenotypes are observed according to the *SDHx* mutated gene.

The SDHD *gene*

SDHD was the first *SDHx* gene identified as being involved in PPGL tumourigenesis [33]. Hereditary PPGL secondary to *SDHD* mutations are inherited in the autosomal dominant mode with a paternal transmission, so the patient phenotype will vary according to the transmitting parent.

Paternal inherited *SDHD* mutations are responsible for cervical PGL (more than 97% of the patients), multiple in two thirds of the cases. The penetrance was evaluated at 86% at the age of 50 years. A family history of PPGL is found in the paternal branch in 60–80% of cases [16,34].

Because of the maternal imprinting, it was considered until recently that maternal inherited *SDHD* mutations were not responsible for the development of PPGL. However, a few cases of violation of the maternal genomic imprinting rule have been described [35]. Recently a prospective study estimated that maternal inherited *SDHD* mutation patients may have a risk of about 5% of developing a PPGL in their life [36].

The SDHB *gene*

SDHB germline mutations predispose to the development of abdominal PGL in 60% of cases, and cervical in 40% of cases. Only 20% of patients have multiple tumours. The average age at PPGL diagnosis is, as for *SDHD*, around 30 years [34]. *SDHB* mutation penetrance is estimated at 50% at age 50 [37].

These penetrance data were recently challenged by a study of 673 *SDHB*-mutated patients, in whom the prevalence was estimated at 22% at 60 years. Unlike previous studies, this study estimated the penetrance in both index cases and their relatives (more than 2 relatives for one index case), which probably explains these lower values [38]. Importantly, mutations in the *SDHB* gene predispose to a metastatic evolution of the disease making them the main predictor of malignancy in PPGL patients [14,39]. Indeed, about half of patients with *SDHB*-mutated PPGL have a metastatic disease, and a germline *SDHB* mutation is found in 36% of patients with a metastatic PPGL [14,16,34]. This metastatic phenotype is associated with an immortalization mechanism. Indeed, in *SDHB* mutated PPGL, genetic or epigenetic somatic alterations have been described in *ATRX* or *TERT* genes which are linked to cellular immortalization [40]. Interestingly, initial studies have shown that *SDHB* metastatic PPGL had a worst prognosis than non-*SDHB* metastatic PPGL [41,42], a concept that has recently been challenged in a large international study performed on 169 patients with metastatic PPGL. In this study, the *SDHB* status was not a worst prognosis parameter anymore [43]. This discrepancy may be explained by the significant increase in the follow up of *SDHB* mutation-carriers that has been established in the past decade [12,43].

The SDHC, SDHA, SDHAF2 *genes*

SDHC, *SDHA* and *SDHAF2* genes are more rarely mutated in patients with PPGL.

SDHC gene mutations predispose to the development of cervical PGL in the majority of cases, with a family history in a quarter of cases [34].

The first *SDHA* mutation was identified in a patient with functional abdominal PGL [44]. In a recent study of 30 patients with *SDHA* related PPGL, 70% of patients had cervical PGL, and 16% a thoracic or abdominal PGL [45].

The first *SDHAF2* gene mutations were described in two families in 2009 and 2010 in the Netherlands and Spain. Members of this family had only single or multiple benign cervical PGL [46]. Since, only 3 additional patients have been described with the same phenotype [47].

SDHx *mutations also predispose to other tumours than PPGL*

SDHx mutations have also been implicated in the genesis of other tumours like kidney cancer and gastrointestinal stromal tumours (GIST). They are thought to be involved in 0.05–0.2% of kidney cancers [48]. It is estimated that two to three percent of patients with an *SDHx* mutation would develop kidney cancer [38]. *SDHx* mutations are also involved in GIST without mutation in the *PDGFRA* and *KIT* genes. They mainly predispose to multiple and malignant GIST occurring in children or young adults [49]. Finally, they have been implicated in pituitary adenomas, although this implication in pituitary tumourigenesis remains debated [50].

Familial PCC and new forms of syndromic PPGL

The familial PCC, TMEM127 *and* MAX *genes*

TMEM127 gene involvement's in PPGL predisposition was demonstrated in 2010 in a large family with PCC [51]. This gene encodes for a negative regulator of the mTOR pathway.

TMEM127 predisposes to epinephrine-producing PCC, which are bilateral in 15–66% of cases and usually appear after 35 years. A family history is found in 15–30% of cases. Penetrance has been estimated to 32% before age 65 [52,53].

This gene has also been implicated in the genetic predisposition to ccRCC [54].

MAX gene encodes a leucine zipper type transcription factor and a member of the MYC/MAX/MXD proteins network, involved in cell proliferation, differentiation and apoptosis [55,56].

MAX mutations predispose to norepinephrine-producing PPGL that develop around 34 years old. The majority of *MAX* mutated patients have an abdominal PGL or a PCC, half of whom being bilateral, either synchronous or metachronous. A family history is found in 40% of cases [57].

The new syndromic PPGL

FH *gene*

The *FH* gene encodes for fumarate hydratase, a Krebs cycle enzyme that catalyzes the step following the succinate dehydrogenase, allowing hydration of fumarate to malate.

FH germline mutations were previously known to be responsible of the HRLCC syndrome (Hereditary Leiomyomatosis and Renal Cell Cancer) or Reed syndrome [58]. Affected patients develop cutaneous leiomyomas in 70% of cases and, rarely, cutaneous leiomyosarcomas. Women have uterine leiomyomas in more than 80% of cases by the age of 30 [59]. Finally, in 15%–19% of cases there is a type 2 papillary renal carcinoma, which has a poor prognosis [59].

FH gene was recently involved in PPGL development. Patients had metastatic or multiple PPGL, in 40% of cases with either no secreting or noradrenaline secretion [32,60]. Interestingly, only one patient had manifestations of HLRCC syndrome.

*PPGL-polycythaemia syndromes (*EPAS1 *and* EGLN1 *genes)*

EPAS1 (also called *HIF2A*) and *EGLN1* (also called *PHD2*) genes encode two proteins involved the hypoxic response. *EPAS1* encodes the alpha subunit of the hypoxia inducible factor HIF2α and *EGLN1* encodes a prolyl-hydroxylase that hydroxylates HIF2α.

EPAS1 germline gain of function mutations and *EGLN1* germline loss of function mutations have been known for many years to be implicated in autosomal dominant congenital polycythaemia [61,62].

Currently, two PPGL patients with polycythaemia carrying a germline mutation in *EGLN1* have been described [63,64].

Somatic gain of function mutations have been found in patients with congenital polycythaemia, somatostatinoma and PPGL [65]. *EPAS1* related PPGL are multiple in half of the cases and occurred at young age [66,67]. Polycythaemia is found in less than half of the cases and single or multiple somatostatinomas are present in one quarter of cases.

All *EPAS1* mutations are found in exons 9 and 12, which encode the two prolines hydroxylated by PHD enzymes, needed for the degradation of HIF2α. Thus, these mutations lead to abnormal stabilization of HIF2α and to an inappropriate activation of the hypoxic response. In addition, these mutations may be present at the tumour level, but also at the state of somatic or constitutional mosaicism. In the latter case, they might be transmissible to the offspring [66].

Somatic mutations of *EPAS1* have very recently been implicated in PPGL that develop in patients with cyanogenic heart disease [68] suggesting that chronic hypoxia may promote their emergence.

New PPGL susceptibility genes

Thanks to the evolution of DNA sequencing technology, many PPGL susceptibility genes have been discovered during the last five years. These genes have been implicated in a very limited number of cases, and for some of them, their involvement remains to be demonstrated in larger studies.

Genes implicated in mitochondrial metabolism

MDH2 *gene*

Malate dehydrogenase type 2 (encoded by the *MDH2* gene) is a mitochondrial enzyme of the Krebs cycle that catalyses the stage after the fumarate hydratase: it oxidizes L-malate to oxaloacetate. This enzyme is also involved in the malate-aspartate shuttle, which is essential for cellular respiration.

Five patients with a *MDH2* germline mutation have been described so far, with precocious forms of PPGL, multiple and metastatic in 40% of cases [7,69].

GOT2 *gene*

In 2017, a gain of function mutation in the *GOT2* gene has been identified in a patient with metastatic multiple PPGL [3]. This gene encodes the mitochondrial glutamic-oxaloacetic transaminase, which is also part of the malate-aspartate shuttle.

SLC25A11 *gene*

SLC25A11 gene encodes the 2-oxoglutarate-malate carrier, which is a part of the malate aspartate shuttle as MDH2 and GOT2. Germline mutations in this gene have been identified in seven patients who presented a metastatic abdominal PGL at an age over 50 years old, in 70% of cases [6]. An eighth patient was recently described in another report [5].

DLST *gene*

In 2019, Remacha et al. have described a new PPGL susceptibility gene, *DLST,* which encodes the dihydrolipoamide S-succinyltransferase. This dihydrolipoamide S-succinyltransferase is the E2 subunit of the mitochondrial alpha ketoglutarate dehydrogenase complex which is a Krebs cycle enzyme catalyzing the conversion of alpha ketoglutarate (αKG) to succinyl-CoA. A recurrent mutation of this new tumour suppressor gene was described in 4 patients with multiple PPGL [5].

Genes implicated in MAPK signaling pathways

MET *gene*

The *MET* oncogene is involved in type 1 papillary renal cell carcinoma predisposition. This gene was known to be mutated at the somatic level in PPGL [70], and recently a germline mutation was found in a family with PCC [2].

MERTK *gene*

Two patients with PPGL and MTC have been recently described as carriers of a germline mutation in this gene, which encodes a tyrosine kinase receptor [2].

Genes implicated in DNA methylation

H3F3A *gene*

A recurrent hot spot mutation in the *H3F3A* gene (a histone subunit) was already implicated in giant cell bone tumours at the mosaic state. The same mutation was found in two patients who had multiple PPGL associated with giant cell bone tumours [2].

DNMT3A *gene*

DNMT3A gene is a DNA methyltransferase that establishes DNA methylation patterns. Two gain of function germline mutations of *DNMT3A* were identified by whole-exome sequencing in two patients one with multiple PPGL and one with familial PPGLs [4].

KIF1Bβ *gene*

Only two germline mutations have been described since 2008 [71,72] in this putative tumour suppressor gene and up to now, its implication in PPGL tumourigenesis has never been formally proven.

Tumour genetics of PPGL

In addition to the germline mutations, tumour mutations have been described in the different PPGL predisposition genes (*VHL, RET, EPAS1, SDHB, NF1*) or in other genes involved in oncogenesis (*HRAS, TP53, CDKN2A, FGFR1*, etc.), explaining up to 30% of PPGL without germline mutations. These tumour mutations increase the number of genetically determined PPGLs to 60–70%, making PPGL the tumour

with the strongest genetic determinism [70]. There is no risk of transmission of these tumour mutations to the offspring.

PPGL genetics and tumourigenesis (Fig. 1)

Recent data from genomics studies have allowed a better understanding of the mechanisms of PPGL tumourigenesis. Indeed, transcriptomic studies have demonstrated that PPGL are classified into three different clusters, reflecting different mechanisms of tumourigenesis [70,73]: the pseudo-hypoxic cluster, the mitogen-activated protein kinase cluster (MAPK) and the Wnt/β-catenine cluster. The first cluster comprises tumours secondary to *SDHx, FH, MDH2, SLC25A11, GOT2, DLST,* and *VHL* genes mutations. This group is characterized by a pseudo-hypoxic signature and increased angiogenesis, due to abnormal stabilization of HIFα transcription factors leading to pseudo-hypoxia. HIF proteins combine a constitutionally expressed subunit (HIFβ) to one of the hypoxia-induced subunits (HIF1α or HIF2α). In physiological and normoxic situations, HIFα are rapidly degraded secondary to two prolines hydroxylation by the PHD proteins, allowing their recognition by VHL and thus their polyubiquitination and degradation in the proteasome. In absence of oxygen, PHDs can no longer ensure the HIFα hydroxylation, which are stabilized and translocated in the nucleus.

SDHx, *FH* and *DLST* mutations lead to the accumulation of succinate, fumarate, and 2 hydroxyglutarate, respectively, which act as competitive inhibitors of the αKG dependent dioxygenases (including PHD), and therefore lead to an abnormal stabilization of HIFα [5,74]. Activation of pseudohypoxia induces the activation of target genes implicated in cell proliferation, angiogenesis, survival and epithelio−mesenchymal transition [31,75].

In addition, epigenetic changes occur in *SDHx* and *FH*-related PPGL. Indeed, succinate and fumarate accumulation also cause the inhibition of the ten-eleven translocation (TET) enzymes, which are αKG dependent dioxygenases involved in DNA demethylation. Moreover their accumulations also inhibits histones demethylases. These mechanisms lead to an overall hypermethylation of DNA and chromatin structural changes. These epigenetics modifications lead to the downregulation of many genes, including tumour suppressor genes and genes involved in metastasis spread repression as well as chromaffin differentiation [32].

The second major mechanism of PPGL tumourigenesis involves the MAPK pathways and the mTOR pathway. These different pathways are activated in *RET, NF1, TMEM127*, *MAX, MET, MERTK* -dependant PPGL. For example, *RET* gene encode tyrosine kinase receptor activating the MAPK pathway. NF1 is involved in regulating the Ras oncogene, the first step of MAPK pathway which regulates the protein kinase B pathway (AKT)/mTOR [70].

Finally, a third cluster has recently been highlighted on the transcriptome data generated by RNA sequencing of the TCGA consortium. This cluster is marked by activation of the Wnt/β-catenine pathway, a pathway involved in the genesis of many tumours, and is driven by a fusion gene including Mastermind Like Transcriptional Coactivator 3 (MAML3) [73].

Genetic implications for PPGL patients

Genetic testing

Because of this strong genetic determinism of PPGL, it is recommended to systematically offer a genetic test to each affected patient [10,11]. Moreover, early knowledge of a positive genetic status improves the clinical outcome of patients carrying an *SDHx* or a *VHL* mutation [12].

Genetic tests were previously performed in a sequential way, and orientated according to the patient's phenotype and in some cases by the results of anti-SDHB, SDHA, MAX, SLC25A11, CAIX immunohistochemistries. Indeed, a negative SDHB immunostaining is in favor of a an *SDHx* gene mutation, while an negative anti-SDHA immunostaining or anti-SLC25A11 point to an *SDHA* or *SLC25A11* mutation, respectively. Finally an anti-MAX negative immunostaining is in favor of

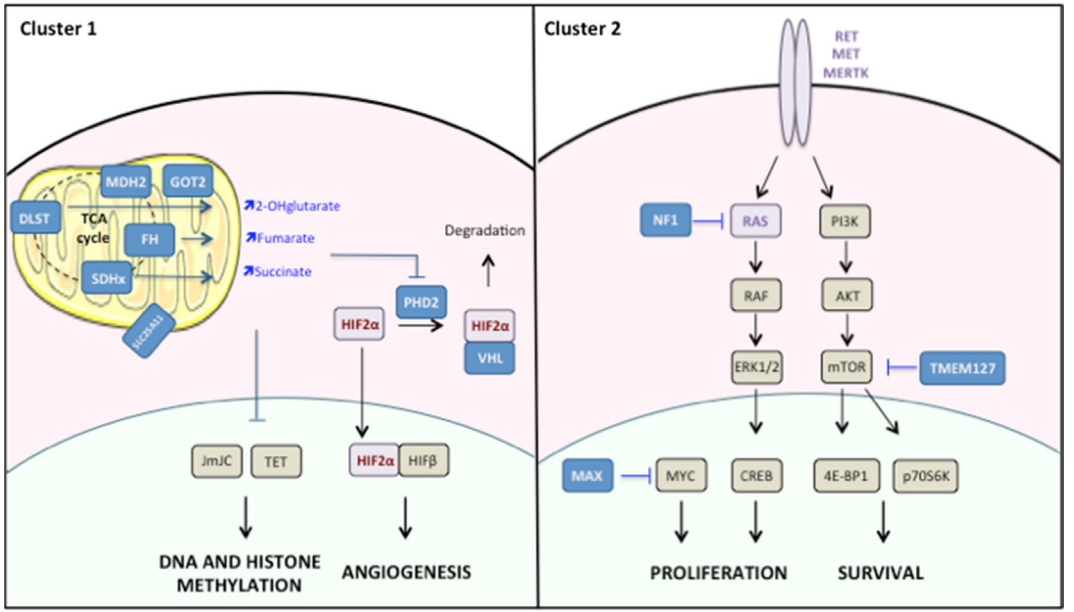

Fig. 1. Schematic representation of tumorigenesis pathway in PPGL, cluster 1 genes on the left and cluster 2 genes on the right. Oncogenes implicated in PPGL tumorigenesis are in purple and tumour suppressor genes are in blue.

truncating mutation of the *MAX* gene and a positive anti-CAIX membranous immunostaining is in favor of a *VHL* mutation [6,44,57,76,77].

This targeted approach is decreasing with the widespread development of Next Generation Sequencing (NGS) technology that allows the sequencing of all PPGL susceptibility genes at once [78]. However, a detailed description of the patient's phenotype and immunohistochemical tests are still useful for the classification, as pathogenic or non-pathogenic, of identified genetic variants which are much more common with NGS. International recommendations were recently published for carrying out the PPGL genetic test by NGS [78].

Follow up of PPGL patients with a positive genetic test

American and European recommendations on the management of PPGL patients have emphasized that patients with a genetic form of PPGL should be followed up appropriately, depending on their genotype [10,11].

The identification of a germline mutation allows the follow up of patients in order to monitor the occurrence of different syndromic lesions, or new PPGL or metastasis [10].

Finally, identification of a mutation in one of these predisposition genes allows to propose a pre-symptomatic screening to relatives and, to include mutation carriers in an adapted follow-up protocol.

Table 2
Follow-up protocol proposal for genetic PPGL.

GENE	Long-life regimen of surveillance in at-risk adults
SDHB	Blood pressure/year
	Metanephrines/year
	Whole body MRI/2 or 3 years
	[^{68}Ga]SSA-PET or FDG-PET if clinical/imagery abnormalities
VHL	Blood pressure/year
	Metanephrines/year
	Optic fundus examination/year
	Central nervous system MRI/2 years
	Whole body MRI/2 or 3 years
SDHD	Blood pressure/year
SDHC	Metanephrines/year
SDHA	Whole body MRI/2 or 3 years
SDHAF2	[^{68}Ga]SSA-PET or FDOPA-PET if clinical/imagery abnormalities
RET	Blood pressure/year
	PTH, calcemia/year
	Thyrocalcitonin/year
	Metanephrines/year
NF1	Blood pressure/year
	Metanephrines if hypertension or adrenal tumours
	Clinical examination for others manifestations
	Optic fundus examination/1 or 2 years for patients <18 yrs
TMEM127	Blood pressure/year
MAX	Metanephrines/year
	Abdominal MRI/2 or 3 years
FH	Blood pressure/year
	Metanephrines/year
	Gynaecological examination/year
	Abdominal MRI/year
HIF2A (EPAS1)	Blood pressure/year
	Metanephrines/year
	Hematocrit/year
	Optic fundus examination/year
	Central nervous system MRI/2 years
	Whole body MRI/2 or 3 years

PET: Positron Emission Tomography, [68 Ga]SSA-PET: gallium-68-labelled somatostatin analogue TEP.

Follow-up recommendations according to the genotype have been proposed [1,79,80] based on expert advices. A proposal of follow-up protocol of these patients is shown in (Table 2).

Conclusion

The knowledge on PPGL genetics as massively progressed over the past 20 years and has allowed a better understanding of PPGL tumourigenesis and above all, a better follow up and managment of patients with genetically determined PPGL and their relatives.

Practice points

- Paragangliomas have a strong genetic susceptibility requiring to offer to all patients a genetic counseling.
- The majority of mutations occur in *SDHD* and *SDHB* genes.
- Germline mutations in the *SDHD* gene predispose to multiple cervical paragangliomas.
- Germline mutations in the *SDHB* gene predispose to metastatic paragangliomas.
- The identification of a mutation in a PPGL susceptibility gene allows the patient to have an adapted follow-up.

Research agenda

- To identify the last PPGL susceptibility genes
- To create specific large cohorts of patients for each susceptibility gene
- Thanks to these cohorts, to edit clinical recommendations for patients' follow-up

Declaration of Competing Interest

The authors have no conflict of interest on the data of this article.

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