REVIEW

GENETICS IN ENDOCRINOLOGY

The genetics of pheochromocytoma: using clinical features to guide genetic testing

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Abstract

Pheochromocytoma is a rare, usually benign, tumour predominantly managed by endocrinologists. Over the last decade, major advances have been made in understanding the molecular genetic basis of adrenal and extra-adrenal pheochromocytoma (also referred to as adrenal pheochromocytoma (aPCA) and extra-adrenal functional paraganglioma (eFPGL)). In contrast to the previously held belief that only 10% of cases had a genetic component, currently about one-third of all aPCA/eFPGL cases are thought to be attributable to germline mutations in at least nine genes (*NF1*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, *MAX* and *VHL*). Recognition of inherited cases of aPCA/eFPGL is critical for optimal patient management. Thus, the identification of a germline mutation can predict risks of malignancy, recurrent disease, associated non-chromaffin tumours and risks to other family members. Mutation carriers should be offered specific surveillance programmes (according to the relevant gene). In this review, we will describe the genetics of aPCA/eFPGL and strategies for genetic testing.

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Background

Adrenal and extra-adrenal pheochromocytoma (aPCA and extra-adrenal functional paraganglioma (eFPGL) respectively) has an incidence of 2–8 cases per million per year. The nomenclature of these tumours can be confusing. The World Health Organization tumour classification defines pheochromocytoma as chromaffin tumours arising from the adrenal medulla, and extra-adrenal tumours as paraganglioma. However, in the published literature the term paraganglioma may be used to refer to tumours derived from sympathetic nervous system or parasympathetic tissue. (Sympathetic tissue is located within the adrenal medulla, prevertebral, paravertebral, thoracoabdominal and pelvic paraganglia or in the reproductive organs, prostate, bladder, liver and organ of Zuckerkandl. Parasympathetic paraganglia are located in the vicinity of the major arteries and nerves, e.g. carotid body, jugular, vagal, tympanic, pulmonary and aortic paraganglioma.) In this review, we refer to aPCA/eFPGL to cover both chromaffin tumours that arise from the adrenal medulla (aPCA) and those functional extra-adrenal tumours derived from sympathetic ganglia (eFPGL). aPCA/eFPGL are usually secretory and typically present with features

of catecholamine excess. In contrast, paragangliomas arising from the parasympathetic nervous system (usually within the head and neck and herein referred to as head and neck parasympathetic paraganglioma (HNPG)) are predominantly endocrinologically inactive.

About 10% of aPCA/eFPGL patients have a family history of pheochromocytoma and up to 25% of apparently sporadic cases with no family history will harbour a germline mutation in an inherited aPCA/eFPGL gene (1). To date, nine genes have been described to be associated with a predisposition to the development of aPCA/eFPGL and/or HNPG (see Table 1). Although clues to inherited syndromic causes of aPCA/eFPGL may be provided by a previous history or family history of relevant tumour (see Table 1), many aPCA/eFPGL genes are associated with incomplete penetrance and/or variable expression (e.g. some *VHL* gene mutations may only be associated with aPCA/eFPGL). In addition to a positive family history of aPCA/eFPGL or evidence of a specific syndrome, the presence of multiple primary tumours is an indicator of genetic predisposition. In sporadic cases with a single tumour, early age at diagnosis, malignancy or extra-adrenal location are all risk factors for the presence of a

Table 1 The common phenotypic characteristics of the nine genes associated with the development of aPCA and eFPGL (see text for further details).

Gene	Clinical phenotype
<i>VHL</i>	von Hippel–Lindau disease – autosomal dominantly inherited predisposition to: aPCA/eFPGL, retinal and cerebellar haemangioblastomas, clear renal cell carcinoma, non-secretory pancreatic neuroendocrine tumours, endolymphatic tumours and visceral cysts (renal, pancreatic and epididymal). Rarely HNPGL. Epididymal cystadenomas
<i>RET</i>	Multiple endocrine neoplasia type 2 (MEN2) – autosomal dominantly inherited predisposition to medullary thyroid carcinoma and aPCA. MEN2A is characterised by medullary thyroid carcinoma, aPCA and primary hyperparathyroidism. MEN2B is characterised by medullary thyroid carcinoma and aPCA and developmental anomalies (marfanoid habitus, mucosal neuromas, etc.). Pheochromocytomas in MEN2 are characteristically adrenal and benign
<i>NF1</i>	Neurofibromatosis type 1 (von Recklinghausen disease) autosomal dominantly inherited predisposition to aPCA/eFPGL, peripheral nervous system tumours (cutaneous, nodular and plexiform neurofibromas), intestinal tumours, gastrointestinal stromal cell tumours, malignant gliomas and juvenile chronic leukaemias. Relatively late (compared with <i>VHL</i> disease and <i>SDHB</i> mutations) mean age of diagnosis (41 years)
<i>SDHA</i>	Autosomal dominantly inherited predisposition to aPCA, eFPGL, HNPGL (though infrequent cause of these tumours) (autosomal recessively inherited juvenile encephalopathy or neonatal cardiomyopathy)
<i>SDHB</i>	Autosomal dominantly inherited predisposition to aPCA, eFPGL, HNPGL and renal cell carcinoma. High frequency of extra-adrenal pheochromocytoma and malignancy
<i>SDHC</i>	Autosomal dominantly inherited predisposition to HNPGL and, less frequently, aPCA and eFPGL
<i>SDHD</i>	Autosomal dominantly inherited predisposition to parasympathetic HNPGL and aPCA and eFPGL. Tumours generally only develop in individuals who have inherited the mutation from their father (i.e. parent-of-origin effects on disease phenotype)
<i>TMEM127</i>	Autosomal dominantly inherited predisposition to aPCA, eFPGL and HNPGL. Relatively late mean age of diagnosis (compared with <i>VHL</i> disease and <i>SDHB</i> mutations)
<i>MAX</i>	Autosomal dominant inheritance with parent-of-origin effects (see text). Increased incidence of bilateral and malignant pheochromocytoma

aPCA, adrenal pheochromocytoma; eFPGL, extra-adrenal functioning sympathetic paraganglioma; HNPGL, head and neck parasympathetic paraganglioma.

germline mutation (though the relevance of these risk factors varies for different genes) but there is no absolute cut off for mutation-positive cases (i.e. a patient with a later onset aPCA will have a low risk of harbouring a detectable mutation but the possibility cannot be completely excluded on clinical grounds).

Clinical and molecular genetic features of specific pheochromocytoma predisposing genes

VHL

von Hippel–Lindau (*VHL*) disease is an autosomal dominant familial cancer syndrome with variable expression and age-dependent penetrance (>90% by the age of 60 years) (2, 3). Germline *VHL* mutations are most commonly associated with retinal angioma, haemangioblastoma and clear cell renal cell carcinoma (average lifetime risk >70% by the age of 60 years) (2). In addition to aPCA/eFPGL, non-secreting pancreatic neuroectodermal tumours occur in ~10% of patients (4). Rarely, HNPGL may occur (<1%) (5). Though renal, pancreatic and epididymal cysts are frequent (and may provide useful clues to the underlying diagnosis) they rarely cause morbidity. Interestingly, the risk of individual tumours can vary according to the germline *VHL* mutation. Although aPCA/eFPGL occur in 15–20% of individuals with *VHL*, the most common *VHL* mutations (deletions, truncating and splice-site mutations) are associated with a low risk of

aPCA/eFPGL, whereas missense mutations that are predicted not to impair the stability of the *VHL* protein have a high risk of aPCA/eFPGL. However, the risk of other tumours is variable (e.g. risk of RCC is low in type 2A *VHL* disease whereas type 2C *VHL* disease is only associated with aPCA/eFPGL) (3, 6, 7). Early detection and treatment of retinal angiomas and renal tumours reduces morbidity and mortality thus the detection of a germline *VHL* mutation as the cause of aPCA/eFPGL can profoundly alter the management of the patient (e.g. initiation of *VHL* disease tumour surveillance protocols) and their family. aPCA/eFPGL in *VHL* disease is characterised by a younger age at diagnosis (mean 28 years) and increased frequency of bilateral or multiple tumours although the risks of malignancy are not elevated (4). As many *VHL*-associated aPCA/eFPGL are detected during routine imaging surveillance, they are more frequently asymptomatic at diagnosis than sporadic aPCA/eFPGL.

RET

Germline activating mutations in the *RET* proto-oncogene cause multiple endocrine neoplasia type 2 (MEN2) and inactivating mutations cause Hirschsprung disease (8). Interestingly, a case of familial pheochromocytoma described in 1886 was shown to result from a germline *RET* mutation 121 years later (9). MEN2 is an autosomal dominantly inherited disorder and is divided into three clinical subtypes, two of which (MEN2A and MEN2B) are characterised by the development of medullary thyroid cancer (MTC) and

aPCA (and hyperparathyroidism in MEN2A and a marfanoid habitus and mucosal neuromas in MEN2B). A number of genotype–phenotype correlations have been described in MEN2. Missense mutations in the intracellular tyrosine kinase domain (e.g. p.Met918Thr) that are associated with a strong transforming activity are associated with MEN2B (MTC and aPCA have an earlier age at onset in MEN2B than MEN2A), whereas missense mutations (e.g. p.Cys634Arg or p.Cys634Tyr) in the extracellular domain that cause abnormal dimerization (and autoactivation) of the mutant proteins have a less transforming activity and cause MEN2A (10–12). Individuals with MEN2A have about a 50% risk of developing aPCA but the mean age at diagnosis of MTC is earlier than that of aPCA (~40 years) and so, compared with individuals with germline *SDHB*, *SDHD* or *VHL* mutations, individuals with MEN2 are less likely to present with sporadic non-syndromic pheochromocytoma. Nevertheless, a germline *RET* mutation can be detected in about 5% of such cases (13). Individuals with MEN2A often develop aPCA (which may be synchronous or metachronous) but eFPGL and malignancy are rare (14).

Neurofibromatosis 1 (von Recklinghausen disease)

Neurofibromatosis 1 (NF1) has been associated with pheochromocytoma since 1910. Cutaneous (localised and plexiform neurofibromas, neurofibrosarcoma) and internal tumours such as aPCA/eFPGL, central nervous system tumours (glioma, astrocytoma and optic gliomas), carcinoid and leukaemia may occur (15). Although NF1 is relatively common (incidence one in 3000 persons), the prevalence of aPCA/eFPGL in NF1 is low (~1%). Therefore, NF1 is not a common diagnosis in aPCA/eFPGL patients (16). The median age at diagnosis of aPCA/eFPGL in NF1 is relatively late (~41 years) and so other features of the disease (e.g. cutaneous café-au-lait spots, axillary freckling, neurofibromas and Lisch nodules) are usually present (so making clinical diagnosis of NF1 straightforward) (17, 18). The *NF1* gene is a large gene (57 exons) and NF1 is associated with a wide variety of, frequently *de novo*, inactivating mutations making genetic analysis difficult. Therefore, although molecular genetic analysis is becoming more available, it is usually not indicated for diagnosis because of the ease of clinical diagnosis (16, 19).

The succinate dehydrogenase complex

Succinate dehydrogenase (SDH) is a heterotetrameric enzyme comprising four subunits (A, B, C and D). An associated protein, SDHAF2, is a highly conserved cofactor of flavin adenine dinucleotide (FAD) that is implicated in flavination of SDHA and is essential for

SDH function. The SDH complex is attached to the inner mitochondrial wall by SDHC and SDHD. SDH has two key roles in cellular energy production: as part of the mitochondrial tricarboxylic acid cycle (catalysing the oxidative dehydrogenation of succinate coupled to the reduction of ubiquinone) and as the complex II component of the electron transport chain.

Loss-of-function mutations in the four SDH complex subunits and SDHAF2 have been demonstrated to cause HNPGL and/or aPCA/eFPGL, though the relative mutation frequency and associated tumour types varies between individual genes.

SDHD mutations were initially associated with HNPGL and subsequently with aPCA/eFPGL (20, 21). Although early studies suggested that *SDHD* mutations were more strongly associated with HNPGL than aPCA/eFPGL (22), a recent report suggests that this is mainly attributable to a very low risk of aPCA/eFPGL with a common *SDHD* missense mutation (p.Pro81Leu) (23). Multifocal tumours are more common with *SDHD* mutations (22). It should be noted that the tumour risk with *SDHD* mutations is for mutations that have been paternally inherited (maternally transmitted mutations have only very rarely been linked with disease and routine surveillance is not indicated in such cases) (24, 25). Mean age at diagnosis of pheochromocytoma in patients with *SDHD* mutations is 35 years (23).

SDHB mutations are an important cause of HNPGL and aPCA/eFPGL (13, 23, 24, 26). In addition, *SDHB* mutations predispose to renal tumours and may present with familial renal cell carcinoma (RCC) (27). Important clinical features of *SDHB* aPCA/eFPGL are a high frequency of extra-adrenal location and malignancy (~20% of mutation carriers will develop malignant disease and up to 50% of patients with a malignant eFPGL harbour a germline *SDHB* mutation) (22, 23, 28–31). Compared with all patients with *SDH* mutations, the overall risk of HNPGL (e.g. carotid body tumours) is higher with *SDHD* mutations whereas the risk of aPCA/eFPGL is higher with *SDHB* mutations (22, 27). Initial reports had suggested a high clinical penetrance for *SDHB* mutations; however, as testing of apparently sporadic cases has become more widespread and asymptomatic relatives of mutation carriers undergo genetic testing, the observed penetrance of *SDHB* mutations has fallen (e.g. 25–40% in non-probands) (32). In addition to renal tumours, *SDHB* mutations may possibly predispose to thyroid tumours (though the absolute risk is small) and *SDHB* and *SDHC* mutations have been found in 12% of individuals with gastrointestinal stromal tumours without *PDGFRA* receptor mutations (33, 34).

SDHC mutations may be present in ~4% of HNPGL patients and though aPCA/eFPGL can occur it is rare (35–38). In the French Paraganglioma cohort, 14 of the 16 patients with *SDHC* mutations had HNPGL and two had a thoracic eFPGL (39).

SDHA mutations were initially described in a biallelic state (homozygous or compound heterozygous) in children with an autosomal recessively inherited juvenile encephalopathy (Leigh syndrome) (40) and mutations in *SDHA* were initially thought to be absent from patients with HNPGL or aPCA/eFPGL. However, recent reports have described heterozygous germline *SDHA* mutations in a small subset of patients with HNPGL and aPCA/eFPGL (41, 42).

TMEM127

Following genetic linkage studies that mapped a novel locus for familial pheochromocytoma to chromosome 2q11, germline mutations were identified in *TMEM127* (43). The presence of loss-of-function mutations and allele loss *TMEM127* pheochromocytoma was consistent with the *TMEM127* acting as a tumour suppressor gene. *TMEM127* encodes a three spanner transmembrane protein that is highly conserved and, although the function of *TMEM127* is not well defined, it has been linked to mTOR signalling (43). In an extensive cohort analysis of 990 individuals with pheochromocytoma or HNPGL, the frequency of *TMEM127* mutations was ~2% (44). In contrast to *VHL* and *SDHB* mutations, patients with mutations in *TMEM127* do not have an early age at diagnosis (median age of 41.5 years). Typically, patients have aPCAs (often bilateral) and malignancy is infrequent (43, 44). The role of genetic testing for *TMEM127* mutations in clinical practice is not well defined as, though mutations are uncommon, they may present in patient groups that are frequently excluded from genetic testing (see later) (44). Furthermore, the recent description of HNPGL and eFPGL in association with *TMEM127* mutations demonstrates how the phenotype associated with inherited pheochromocytoma gene mutations can continue to evolve (45).

MAX

Recently, germline inactivating mutations in *MAX* were detected by exome sequencing (46). Loss of wild-type *MAX* was also noted in tumour DNA and immunostaining revealed loss of *MAX* expression consistent with a tumour suppressor function. *MAX* is a key component of the MYC-MAX-MXD1 network that regulates cell proliferation and differentiation and there is crosstalk between this network and the mTOR pathway (to which *TMEM127* has been linked (see above)). Interestingly, evidence was found that paternal transmission of the gene was necessary for tumour development (as with *SDHD* and *SDHAF2*). Most cases of *MAX*-associated pheochromocytoma were bilateral, confirming the association between genetic abnormalities and multiple tumours. An association with malignancy was also found.

Other genes

Two apparently very rare causes of pheochromocytoma are mutations in *KIF1B* and *PHD2*. Mutations in these genes have been described in only a few or single families, respectively (47–50), and neither gene is routinely analysed in clinical practice. Mutations in *SDHAF2/SDH5* have been described in association with HNPGL but, to date, not with pheochromocytoma (51, 52). The *SDHAF2* gene maps to chromosome 11q13 and, as with *SDHD* (11q23), there are parent-of-origin effects on expression such that tumour development only occurs after paternal inheritance (51, 52).

The molecular pathophysiology of inherited pheochromocytoma

It is clear that many genes are implicated in the pathogenesis of inherited pheochromocytoma. However, gene expression studies have highlighted potential shared mechanisms of pathophysiology. For example, aPCA/eFPGL associated with germline mutations in *VHL*, *SDHD* and *SDHB* are associated with activation of hypoxic gene response pathways, whereas tumours associated with *NF1* and *RET* mutations do not show a hypoxic gene signature but do show dysregulation of genes implicated in adrenergic metabolism, protein synthesis and kinase signalling (53–55). It was estimated that about 30% of sporadic aPCA and eFPGL have a similar gene expression signature to *VHL/SDHX* tumours and the other 70% to *NF1/RET* (53). Interestingly, the differences in gene expression profiles can be correlated with the tendency of *VHL* and *SDHX* tumours to produce mainly noradrenaline, and *RET/NF1* tumours to be adrenergic (56). Recently, Burnichon *et al.* (55) have demonstrated that the gene expression profiling can be used to identify which subset of sporadic tumours are likely to harbour somatic *VHL* or *RET* mutations and so provide a basis for potential personalised therapies.

Genetic testing in pheochromocytoma patients

The identification of inherited pheochromocytoma genes provided the opportunity to define the frequency of specific gene mutations in both familial cases and in apparently non-syndromic sporadic cases. Unexpectedly, mutation analysis of *RET*, *SDHB*, *SDHD* and *VHL* revealed mutations in up to 25% of sporadic cases suggesting that at least a third of patients with pheochromocytoma had inherited disease (13). The implications of identifying a germline mutation are profound – not only may close relatives be at risk for familial disease but the proband is generally placed at

increased risk of developing further pheochromocytoma tumours and, depending on the specific gene mutation, there may be a risk of developing other tumour types (see Table 1). Although it has been suggested that all patients with pheochromocytoma should be offered genetic testing, such a policy is (with conventional mutation detection methodologies) expensive (e.g. a recent estimate for testing *SDHB*, *SDHC*, *SDHD*, *VHL* and *RET* was \$4100 (57)), and so more targeted screening has been advocated. Clinical features that influence the odds of detecting a mutation in an individual case will include whether there is: i) a personal or family history to indicate a syndromic cause (e.g. MTC, HNPGL and haemangioblastoma); ii) a positive family history for pheochromocytoma; iii) multiple primary pheochromocytomas; iv) malignancy; v) extra-adrenal location; and vi) age at diagnosis (generally inherited tumours occur at an earlier age than non-inherited). In the seminal study by Neumann *et al.* (13), 70% of individuals with pheochromocytoma aged <10 years had a detectable mutation (in *SDHB*, *SDHD*, *RET* or *VHL*) compared with 8% of those who presented after age 40 years.

If a targeted approach to mutation analysis is to be pursued then it is generally agreed that those with a personal or family history of a specific syndromic cause and, in apparently non-syndromic cases, those with a positive family history for pheochromocytoma, or multiple or bilateral tumours, should be analysed. It is usual to test individual genes sequentially and the order of testing can be individualised according to the likelihood of a syndromic cause (e.g. *RET* if there is a family history/personal history of MTC, *SDHB/D* if a HNPGL) or, in apparently non-syndromic cases with familial or multicentric pheochromocytoma, the presence of extra-adrenal or malignant tumours would favour starting with *SDHB* analysis (but *VHL* if an aPCA). There are no generally agreed criteria regarding which patients with apparently non-syndromic sporadic pheochromocytoma should be offered genetic testing for most frequently mutated genes (*SDHB*, *SDHD*, *VHL* and *RET*) (NF1 genetic testing is only indicated if there is clinical evidence of the disorder). Clearly, the more targeted mutation analysis is designed to be, the more cost-effective (in terms of expenditure per mutation detected) but less sensitive it will be. We suggest that all patients with malignant pheochromocytoma should be offered testing for *SDHB*, *VHL* and *SDHD* mutations as about 40–50% of such patients will have a detectable mutation (~35, 5 and 1% respectively). For patients with sporadic non-syndromic ePGLs the mutation detection rate is also high and we would also suggest testing *SDHB*, *VHL* and *SDHD* in such cases. For patients with a single benign aPCA it is generally agreed that the age at diagnosis be used to prioritise testing – though the precise age cut off has varied between investigators. In the largest study yet reported, Erlic *et al.* (57) suggested that an age cut off

at 45 years would appreciably reduce the costs of genetic testing at the expense of only missing a relatively small number of mutation-positive cases (<5%) and so, when budgets for genetic testing are limited, it seems reasonable to restrict genetic testing (*VHL*, *RET*, *SDHB* then *SDHD*) to these younger cases (see Fig. 1). As testing for *TMEM127* and *MAX* becomes more widely available then the indications for including testing for these genes will need to be incorporated into genetic testing protocols.

Within 5 years a number of scientific research and technological advances are likely to make it entirely feasible to evaluate all pheochromocytoma patients for the risk of inherited disease. Immunohistochemical analysis has been used to identify tumours with loss of *SDHB* and *SDHA* expression that can then be prioritised for mutation analysis. Thus, in a series of 220 pheochromocytomas, van Nederveen *et al.* (58) found a 100% sensitivity and 84% specificity for the association of *SDHB* immunohistochemistry and the presence of a detectable mutation. Likewise, *SDHA* immunohistochemistry was used to identify cases for *SDHA* mutation analysis (42). Such immunohistochemical information (and we note that aPCA/eFPGL

Figure 1 Example of targeted mutation analysis protocol for diagnostic testing of major genes (*RET*, *SDHB*, *SDHD* and *VHL*) in patients presenting with adrenal pheochromocytoma or ePGL extra-adrenal functioning sympathetic paraganglioma and no evidence of a specific pheochromocytoma syndrome (see text for details).

associated with MAX mutations demonstrated loss of MAX expression (46)) might be combined with other biomarkers (e.g. evidence of tumour pseudohypoxia) to develop more sensitive and specific strategies for targeting mutation analysis (53–55, 58, 59). In addition, advances in sequencing technologies (e.g. exon capture and targeted resequencing by second generation massively parallel sequencing) will reduce greatly the cost of genetic diagnosis and so allow comprehensive analysis for all (i.e. currently known and those yet to be identified) inherited pheochromocytoma genes (60). Hence, clinicians should bear in mind that individuals who appear likely to have inherited disease but do not have a mutation in a currently known gene should have DNA banked to allow for future mutation analysis. However, it should be noted that whilst comprehensive genetic analysis will increase the identification of inherited predisposition cases, it will also identify rare genetic variants that might not be easily classified as a pathogenic mutation or a benign polymorphism and in such cases costly further investigations may be required. Thus, it is important to take into account all available clinical and laboratory information to advise on optimum management.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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