15 YEARS OF PARAGANGLIOMA

The association of pituitary adenomas and phaeochromocytomas or paragangliomas

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Abstract

The combination of pituitary adenomas (PA) and phaeochromocytomas (phaeo) or paragangliomas (PGL) is a rare event. Although these endocrine tumours may occur together by coincidence, there is mounting evidence that, in at least some cases, classical phaeo/PGL-predisposing genes may also play a role in pituitary tumorigenesis. A new condition that we termed ‘3PAs’ for the association of PA with phaeo and/or PGL was recently described in patients with succinate dehydrogenase mutations and PAs. It should also be noted that the classical tumour suppressor gene, MEN1 that is the archetype of the PA-predisposing genes, is also rarely associated with phaeos in both mice and humans with MEN1 defects. In this report, we review the data leading to the discovery of 3PAs, other associations linking PAs with phaeos and/or PGLs, and the corresponding clinical and molecular genetics.

Key Words
- pituitary
- phaeochromocytoma
- paraganglioma
- SDH
- pathogenesis

Introduction

Pituitary adenomas (PA) and phaeochromocytomas/paragangliomas (phaeo/PGL) are relatively rare tumours. The prevalence of symptomatic PA in the general population is around 1 in 1000 (Daly et al. 2006, Fernandez et al. 2010). The prevalence of pituitary incidentalomas is much higher and reaches over 20% in some imaging series (Ezzat et al. 2004) although the clinical and pathological significance of such lesions detected on imaging performed for an unrelated reason is debatable. Phaeo/PGL are less common, with a prevalence ranging from 1:2500 (Mazzaglia 2012) to 1:6667 (Eisenhofer et al. 2013). Up to 40% occur within increasingly well-defined genetic syndromes (Raygada et al. 2011). Phaeos account for ~5% of all adrenal incidentalomas (Young 2000), although they are frequently first detected on imaging (Motta-Ramirez et al. 2005) and merit definitive management regardless of the method of their discovery.

The coexistence of two rare endocrine tumours within the same patient may be either entirely coincidental or a result of a common pathogenesis. Possible explanations include: a phaeo/PGL-predisposing mutation also causing...
PAs; a PA-predisposing mutation also causing phaeo/PGL; mutations in two different genes; a mutation in a novel gene causing both pathologies; and ectopic hormone secretion by a phaeo/PGL mimicking a PA.

Ever since the first description of coexisting PA and phaeo/PGL (Iversen 1952), there have been arguments for and against a connection (Schimke 1990). Converting association into causality has only begun to occur in the last few years due to the identification of the seemingly ever increasing multiple phaeo/PGL and PA-predisposing genes. Using a combination of tumour DNA analysis to look for loss of heterozygosity (LOH) at specific loci and immunohistochemistry for their related gene products, it has been possible to begin to identify causal relationships (Xekouki et al. 2012, Papathomas et al. 2014, Dénes et al. 2015). Indeed, the term ‘3Pas’ representing the association of three tumour types – pituitary, phaeo and PGL – has been coined to identify this clinical scenario (Xekouki et al. 2015).

A total of 72 patients have been described in the published literature who harbour both a phaeo/PGL and a PA. Twenty-one (29%) are patients with identified mutations in predisposing phaeo/PGL or PA genes (Table 1), 23 (32%) are in patients with a personal or family history that is suggestive of a hereditary endocrine syndrome (Table 2) and 28 (39%) are isolated cases (Table 3). These figures correspond to cases in which have not undergone genetic testing.

This review examines the evidence for the role of the known genetic determinants in the association of PAs with phaeo/PGLs, as well as highlighting potential masquerading pathologies.

**Phaeo/PGL-predisposing genes**

**Succinate dehydrogenase**

The succinate dehydrogenase (SDH) complex consists of four subunits A, B, C and D. The hydrophilic A and B subunits form the catalytic core of the enzyme and contain the substrate binding site for succinate whilst the hydrophobic C and D subunits anchor the complex to the inner mitochondrial membrane as mitochondrial complex II. SDH is part of both the tricarboxylic acid (TCA) cycle and the electron transport chain. It catalyses the succinate to fumarate step and transfers electrons to the ubiquinone pool. Disruption of SDH function leads to succinate accumulation which inhibits prolyl hydroxylases (PHDs) which are unable to hydroxylate the transcription factor hypoxia-inducible factor 1 alpha (HIF1α) resulting in the transcription of HIF-responsive genes and a state of tissue pseudohypoxia (Selak et al. 2005). Succinate inhibits additional α-ketoglutarate dependent enzymes including histone demethylases (Smith et al. 2007) resulting in potential epigenetic modification (Letouzé et al. 2013). Disrupting the electron transport chain results in superoxide generation which also contributes to PHD inhibition (Gerald et al. 2004), although is insufficient to be genotoxic in its own right (Smith et al. 2007).

Mutations in any of the four genes encoding the SDH subunits (SDHx; SDHA, SDHB, SDHC, SDHD) or its associated assembly factor (SDHAF2) can result in hereditary phaeo/PGL. SDHx mutations are also responsible for some cases of Carney-Stratakis syndrome (McWhinney et al. 2007) and polymorphisms have been related to Cowden-like syndrome, although this association requires further elucidation (Ni et al. 2008).

The presence of SDHx mutations in PAs is rare in both unselected PA (Gill et al. 2014, Papathomas et al. 2014) and SDHx mutation carrier cohorts (Benn et al. 2006) but are more likely if phaeo/PGL are also present or if there is a positive family history of phaeo/PGL (Xekouki et al. 2015).

Following a case report of an SDHB mutation positive family with PGLs and macroadenomas in 2009 (Brahma et al. 2009), Xekouki et al. (2012) demonstrated loss of heterozygosity at the SDHD locus along with reduced SDHD protein expression in a growth hormone (GH)-secreting macroadenoma in a patient with a germline SDHD mutation.

In the largest study to date to look at the co-existence of phaeo/PGL and PA, Dénes et al. (2015) identified eight patients with SDHx mutations or variants and both phaeo/PGL and PA within an international cohort of 19 patients. They also demonstrated that SDHx related PAs have a unique and specific histological phenotype characterised by intracytoplasmic vacuoles (Fig. 1), although the exact nature of the vacuoles requires further elucidation and holds promise in providing additional information to unravel its pathogenesis.

**SDHB**

Mutations in the SDHB gene give rise to Familial Paragangliomas Type 4 (OMIM #115310) with a predominance of paragangliomas displaying increased malignant potential (Neumann et al. 2004, Timmers et al. 2007).

Six cases of patients with an SDHB mutation who have both a PA and phaeo/PGL have been reported (Table 1; Dénes et al. 2015, Xekouki et al. 2015). All but two patients had functional PAs, one of which was a macroadenoma. Five...
<table>
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<th>Patient no.</th>
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<th>Size</th>
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<th>Age</th>
<th>Phaeo/PGL Type</th>
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**Family history**

- Aunt, uncle, brother
- HNPGL
- AIP & CDKN1B polymorphism
- MEN1 c.1452delG
- MEN1 c.196_200delAG-CCC--> frameshift (pathogenic), polymorphism C423T --> no amino acid change
- MEN1 p.Lys119Ter
- MEN1 c.320del2
- RET p.Cys18Ser
- RET c.1900T>G

**Mutation**

- SDHD c.242C>T
- p.Pro81Leu
- SDHD c.298_301del, premature stop at codon 133
- AIP & CDKN1B polymorphism
- MEN1 c.1452delG
- p.Thr557Ter
- MEN1 c.196_200delAG-CCC--> frameshift (pathogenic), polymorphism C423T --> no amino acid change
- MEN1 p.Lys119Ter
- RET WT
- MEN1 c.320del2
- RET p.Cys18Ser
- RET c.1900T>G

**Other info**

- Bilateral HNPGL
- HNPGL, abdo and pelvic PGL, bilateral Phaeo
- PA: LOH at SDHD locus, reduced SDHD protein
- Abdominal PGL, breast cancer, adrenal adenoma, uterine leiomyoma, parathyroid adenomas, thymic carcinoid, lung hamatoma; raised IGF-1, prolactin, UFC
- HPTH, pNET
- HPTH, pNET, adrenal adenoma
- HPTH, MTC

**Reference**

- Varsavsky et al. (2013)
- Xekouki et al. (2012)
- Dénès et al. (2015)
- Jeong et al. (2014)
- Langer et al. (2002)
- Dackiw et al. (1999)
- Heinlen et al. (2011)
- Naziat et al. (2013)

M, male; F, female; NFPA, non-functional pituitary adenoma; PRL, prolactinoma; GH, acromegaly; ACTH, Cushing’s disease; PA, pituitary adenoma; Macro, macroadenoma; Micro, microadenoma; DA, dopamine agonist; RT, radiotherapy; SSA, somatostatin analogue; Phaeo, phaeochromocytoma; PGL, paraganglioma; HNPGL, head and neck paraganglioma; LOH, loss of heterozygosity; PTC, papillary thyroid cancer; GIST, gastrointestinal stromal tumour; pNET, pancreatic neuroendocrine tumour; MTC, medullary thyroid carcinoma; HPTH, hyperparathyroidism; IGF-1, insulin-like growth factor 1; UFC, urinary free cortisol; NK, not known.
## Table 2

Patients with pituitary adenoma and phaeochromocytoma/paraganglioma without identified mutations but with suspicious features

<table>
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*Family history:*
- SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B
- SDHB
- SDHA
- SDHA-D
- AIP
- MEN1
- RET
- PTEN polymorphisms
- HNPGL
- Features of Cowden syndrome
- Abdominal PGL
- Bilateral HNPGL
- Bilateral phaeo
- Lipoma, metastatic PTC
- Lipoma, pNet
- Clinical features NF1
- Abdominal, HN, cardiac PGLs
- Lipoma, pectus excavatum, pleomorphic parotid adenoma. Acromegaly cured by adrenalectomy
- Bilateral phaeo
- Abdominal PGL
- Malignant phaeo
- HPTH
- HPTH, MTC

*Genetics tested:*
- SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B
- SDHB
- SDHA
- SDHA-D
- AIP
- MEN1
- RET
- PTEN polymorphisms
- HNPGL
- Features of Cowden syndrome

*Other info:*
- Abdominal PGL: no LOH at SDHA locus, intracytoplasmic vacuoles, SDHA and B staining preserved
- Abdominal PGL
- Wilms tumour, liposarcoma, renal oncocytoma;
- PA: no LOH at SDHA locus, intracytoplasmic vacuoles, SDHA and B staining preserved
- Bilateral HNPGL
- Bilateral phaeo
- Lipoma, metastatic PTC
- Lipoma, pNet
- Clinical features NF1
- Abdominal, HN, cardiac PGLs
- Lipoma, pectus excavatum, pleomorphic parotid adenoma. Acromegaly cured by adrenalectomy

*Reference:*
- Boguszewski et al. (2012), Dénes et al. (2015)
- Dénes et al. (2015)
- Xekouki et al. (2015)
- Xekouki et al. (2015)
- Parghane et al. (2014)
- Efstathioudou et al. (2014)
- Sisson et al. (2012)
- Gatta-Cherifi et al. (2012)
- Siison et al. (2012)
- Zhang et al. (2011)
- Baughan et al. (2001)
- Teh et al. (1996)
- Carty et al. (1998)
- Bertrand et al. (1987)
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M, male; F, female; NFPA, non-functional pituitary adenoma; PRL, prolactinoma; GH, acromegaly; Chrom, chromophobic; Macro, macroadenoma; Micro, microadenoma; DA, dopamine agonist; RT, radiotherapy; SSA, somatostatin analogue; Phaeo, phaeochromocytoma; PGL, paraganglioma; HNPGL, head and neck paraganglioma; PTC, papillary thyroid cancer; GIST, gastrointestinal stromal tumour; pNET, pancreatic neuroendocrine tumour; MTC, medullary thyroid carcinoma; HPTH, hyperparathyroidism; NK, not known; MEN1, multiple endocrine neoplasia type 1; NF1, neurofibromatosis type 1.

*Single nucleotide polymorphism with a frequency of 3.5% (Bayley et al. 2005).*

*Single nucleotide polymorphism with a minor allele frequency of 0.2% and a genotype frequency of 0.5% (Abecasis et al. 2012).*
## Table 3

<table>
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<tr>
<th>Patient no.</th>
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<th>Size</th>
<th>Treatment</th>
<th>Age</th>
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M, male; F, female; NFPA, non-functional pituitary adenoma; PRL, prolactinoma; GH, acromegaly; Macro, macroadenoma; Micro, microadenoma; DA, dopamine agonist; RT, radiotherapy; SSA, somatostatin analogue; Phaeo, phaeochromocytoma; PGL, paraganglioma; HNPGL, head and neck paraganglioma; NK, not known.
of the six patients had PGL. An additional three patients with SDHB mutations with a PA but without a phaeo/PGL have been described (Benm et al. 2006, Dénès et al. 2015). LOH at the SDHB locus and intracytoplasmic vacuoles were identified in two of the three PAs in which it was examined. A patient with a microprolactinoma and a head and neck PGL as well as multiple features of Cowden syndrome (papillary thyroid cancer, macrocephaly, skin plaques, fibrocystic mammary disease, uterine leiomyofibroma) in association with an SDHB variant has also been described (Table 2; Efstathiou et al. 2014). This synonymous SDHB variant occurs with a population frequency of 3.5% in the TCA Cycle Gene Mutation Database and is not thought to be pathogenic (Bayley et al. 2005).

Heterozygous Sdhb knock out mice have abnormal pituitary morphology, developing hyperplastic pituitaries with cellular abnormalities including intranuclear inclusions, altered chromatin nuclear pattern, abnormal mitochondria and increased HIF1α expression. Circulating pituitary hormone levels were not significantly affected (Xekouki et al. 2015).

SDHD

Mutations in the SDHD gene cause Familial Paragangliomas Type 1 (OMIM #168000), which features a high prevalence of head and neck PGL but also phaeos (Neumann et al. 2004, Ricketts et al. 2010).

Five patients with SDHD mutations and both a PA and phaeo/PGL have been reported (Table 1; Xekouki et al. 2012, Xekouki et al. 2015, Varsavsky et al. 2013, Papathomas et al. 2014). All patients had functional macroadenomas and head and neck PGLs (two had phaeos in addition). Loss of heterozygosity at the SDHD locus was demonstrated in the PA of one patient (Xekouki et al. 2012) along with reduced SDHD protein content by western blot and immunohistochemistry. Of two patients identified by Papathomas et al. (2014) one PA displayed LOH at the SDHD locus and negative SDHB staining whilst one did not.

Heterozygous Sdhd knockout mice do not develop PA or phaeo/PGL (Piruat et al. 2004, Bayley et al. 2009) but have carotid body overactivity and glomus cell hyperplasia and hypertrophy, which is a potential prelude to tumour formation (Piruat et al. 2004).

SDHC

Mutations in the SDHC gene cause Familial Paragangliomas Type 3 (OMIM #605373) in which head and neck PGLs predominate (Schiavi et al. 2005).
Two cases of a PA and phaeo/PGL occurring in individuals with SDHC mutations have been described (López-Jiménez et al. 2008, Dénes et al. 2015). Both had a head and neck PGL and a macroprolactinoma treated with dopamine agonist therapy. As a result, no tumour tissue is available for analysis.

**SDHA**

Mutations in the SDHA gene cause the rare Familial Paragangliomas Type 5 (OMIM #614165 (Burnichon et al. 2010).

Germline SDHA mutations were described in a patient with a head and neck PGL and her son with a non-functional PA (NFPA) (Dwight et al. 2013). Immunohistochemistry (IHC) for SDHA was negative in both the proband’s PA and his mother’s PGL.

Dénes et al. (2015) identified two patients with PA and phaeo/PGL with SDHA variants (Tables 1 and 2). One was a synonymous variant with a population frequency of 0.5% (Abecasis et al. 2012) in a patient who in addition to an abdominal PGL and NFPA also had a Wilms tumour, retroperitoneal liposarcomas and a renal oncocytoma. The pituitary adenoma retained staining for SDHA and SDHB and there was no loss of heterozygosity at the SDHA locus, although intracytoplasmic vacuoles were observed. The second patient had a truncating variant in the SDHA gene with a population frequency of 0.3% and is thought to be probably pathogenic with a very low penetrance (Bayley et al. 2005). In addition, this patient also had a VHL mutation which is discussed elsewhere.

**SDHAF2**

Mutations in SDHAF2 cause Familial Paraganglioma type 2 (OMIM #601650) which is characterised by head and neck paragangliomas (Hao et al. 2009).

A single patient with an SDHAF2 variant and PA and phaeo/PGL has been reported (Table 1). He was an elderly man with a somatotroph macroadenoma and head and neck PGL; no tumour tissue was available for analysis (Dénes et al. 2015). The variant is located in the 5' UTR and has not been described in a reference population (Abecasis et al. 2012).

Thus there is increasing evidence that SDHx mutations may play a role in pituitary tumorigenesis in patients with germline mutations and appear to give rise to a specific PA phenotype. Further characterisation of this may provide insight into the mechanisms of pathogenesis.

**Von Hippel-Lindau**

Von Hippel-Lindau syndrome (VHL; OMIM #193300) is an inherited cancer syndrome characterised by haemangioblastomas of the central nervous system, retinal haemangiomas, renal cysts and cancer, pancreatic cysts and pancreatic neuroendocrine tumours (NETs), and phaeo. It is caused by heterozygous mutations in the VHL tumour suppressor gene on chromosome 3p25 which encodes protein VHL (pVHL). The VHL protein has a number of functions that have been implicated in tumorigenesis. Its best-established role is as an E3-ubiquitin ligase that targets the a-subunits of HIF for degradation by the proteasome. When this does not occur, as is the case with mutant pVHL, HIFz heterodimerizes with HIFb and translocates into the nucleus resulting in upregulation of the transcription of multiple genes involved in angiogenesis, glycolysis and cell proliferation.

Pituitary adenomas are not an established feature of VHL syndrome although a role for pVHL in pituitary tumorigenesis has been postulated. VHL protein is expressed in the cytoplasm of normal pituitary cells but is more variably distributed within different PA subtypes. Somatotropinomas, the least vascularized tumour type, displayed frequent predominantly nuclear staining for pVHL suggesting a possible inhibitory role for pVHL in pituitary angiogenesis (Vidal et al. 1999). In a study of 30 NFPAs, low expression of pVHL was associated with increased vascular endothelial growth factor expression and an increased risk of tumour recurrence or regrowth but not with proliferative index (Shimoda et al. 2013).

Only two cases of a PA in the context of a VHL mutation have been described. A 15-year-old boy with a pathogenic VHL mutation developed an aggressive and recurrent GH/prolactin secreting macroadenoma that required multi-modal intervention (Tudorancea et al. 2012). Examination of the PA did not reveal intracytoplasmic vacuoles and there was no LOH at the VHL locus, although intracytoplasmic vacuoles were observed. The second patient had a prolactinoma and phaeo, and variants in both VHL and SDHA (Dénes et al. 2015). The VHL variant is pathogenic (D’Elia et al. 2013). The SDHA variant is truncating and classed as probably pathogenic (Bayley et al. 2005), but as no PA tissue was available the role of either variants in the PA pathogenesis is unknown.

The low number of reported cases of PAs in VHL is somewhat surprising given the frequency with which patients undergo regular surveillance imaging of the
brain and thus have the potential for incidentalomas to be discovered, suggesting that this association of VHL and PA may not represent a syndrome and could be coincidence. However, this association has not been studied formally.

**MEN2**

MEN2A (OMIM #171400) and 2B (#162300) are autosomal dominantly inherited syndromes resulting from gain-of-function mutations in the rearranged during transfection (RET) proto-oncogene on chromosome 10q11, which is also responsible for Familial Medullary Thyroid Carcinoma (FMTC, OMIM #155240). MEN2A and 2B consist of medullary thyroid cancer (MTC), phaeo and hyperparathyroidism in addition to marfinoid features and mucosal neuromas in MEN2B (also previously known as MEN3). The RET protein is a tyrosine kinase receptor for the glial cell line-derived neurotrophic factor (GDNF) family of ligands. There is a close genotype-phenotype correlation in MEN2.

RET is expressed in pituitary somatotrophs (Urbano et al. 2000) and somatotropinomas (Japón et al. 2002), and its knockout in mice, although lethal, results in an enlarged pituitary gland due to somatotroph hyperplasia (Cañibano et al. 2007). It interacts with aryl hydrocarbon receptor-interacting protein (AIP) conveying possible synergistic activity in regulating somatotroph proliferation and tumorigenesis (Vargiolu et al. 2009). Despite this potential role in pituitary tumorigenesis, neither somatic (Yoshimoto et al. 1999) nor pathogenic germline (Heliövaara et al. 2011) RET mutations have been identified in PAs.

Two cases of co-existing phaeo/PGL and PA in patients with confirmed RET mutations (Table 1; Heinlen et al. 2011, Naziat et al. 2013) have been reported. In both cases the PAs were functional (one Cushing’s, one acromegaly) but no tumour analysis was performed. A further four cases of co-existing phaeo/PGL and PA have been reported in patients with a clinical diagnosis of MEN2 but without a proven RET mutation (Table 2; Steiner et al. 1968, Wolf et al. 1972, Anderson et al. 1981, Bertrand et al. 1987). In these patients there were no PGLs, and all but one PA was functional.

One additional case of a patient with a confirmed RET mutation developing a PA without phaeo/PGL has been reported (Saito et al. 2010), although no tumour analysis was undertaken.

Thus, although PAs have been described in MEN2 patients including some with confirmed RET mutations, there is insufficient evidence available at present to conclude whether it plays a role in pituitary tumorigenesis.

**Neurofibromatosis type 1**

Neurofibromatosis type 1 (NF1, OMIM #162200) is an autosomal dominantly inherited neurocutaneous syndrome caused by mutations in the neurofibromin 1 gene and features café au lait spots, Lisch nodules, neurofibromas and optic pathway gliomas. Phaeochromocytoma is an associated tumour type and it occurs in up to 5% of patients with NF1 (Gutmann et al. 1997).

No cases have been reported of a co-existing phaeo/PGL and PA in a patient with NF1. Six reports of a PA in NF1 have been described (Boudin et al. 1970, Barberis et al. 1979, Adeloye 1979, Pinnamaneni et al. 1980, Nakajima et al. 1990, Kurozumi et al. 2002) although none have undergone further analysis of the PAs and a clinical rather than genetic diagnosis of NF1 was made in all cases.

**Other phaeo susceptibility genes**

Pituitary adenomas have not been reported in patients with mutations in the most recently discovered phaeo/PGL susceptibility genes: MYC-associated factor X (MAX), transmembrane protein 127 (TMEM127), kinesin family member 1B (KIF1B), endothelial PAS domain protein 1 (EPAS1), PHD 1 and 2 (PHD1, PHD2), fumarate hydratase (FH), or malate dehydrogenase 2 (MDH2).

**Pituitary adenoma-predisposing genes**

**MEN1**

MEN1 (OMIM #131100) is an autosomal dominantly inherited syndrome comprising of tumours of the parathyroids, endocrine pancreas and pituitary. It arises due to mutations in the tumour suppressor gene MEN1 which encodes menin, a 610 amino acid nuclear scaffold protein with roles in cell division (Schnapp et al. 2004), genome stability (Hughes et al. 2004) and transcription regulation (Agarwal et al. 1999).

Although described, the association of phaeos with MEN1 is rare, being present in <1% of large series (Skogseid et al. 1992, Burgess et al. 1996, Trump et al. 1996, Marx et al. 1998, Langer et al. 2002, Gatta-Cherifi et al. 2012). The prevalence of phaeos is significantly higher, up to 7%, in the Men1 heterozygous knockout mouse model (Crabtree et al. 2001).

Only four cases of co-existing phaeo/PGL and PA have been reported in patients with MEN1 mutations (Table 1; Dackiw et al. 1999, Langer et al. 2002, Jeong et al. 2014).
Dénès et al. 2015); three had a phaeo, one had an abdominal PGL. Loss of heterozygosity at the MEN1 locus combined with absent menin staining in the phaeo sample was demonstrated in one of these cases (Fig. 2; Dénès et al. 2015) suggesting a role in pathogenicity.

A number of other cases have been reported in which patients have both phaeo/PGL and PA with a clinical suspicion of MEN1 but without genetic confirmation, mainly because genetic testing was not performed or available at the time of publication (Table 2).

Phaeo/PGL without PAs have been reported three times in patients with confirmed MEN1 mutations (Dackiw et al. 1999, Jamilloux et al. 2013, Dénès et al. 2015). In one of these cases, LOH at the MEN1 locus and weak menin staining was identified in the phaeo (Deñes et al. 2015).

Other cases of phaeo (Trump et al. 1996, Marx et al. 1998) and PGL (Hashimoto et al. 1986) have been described in patients with a clinical diagnosis of MEN1 but in whom genetic information is not available.

The existence of an MEN1/2 overlap syndrome has previously been proposed and there are numerous examples of phaeo/PGL being associated with pancreatic NETs (Tateishi et al. 1978, Carney et al. 1980, Zeller et al. 1982, Tamasawa et al. 1994), although without additional germline or tumour genetic data.

Thus there is evidence that phaeos can form part of the MEN1 syndrome and that in some cases, at least, MEN1 mutations contribute to pathogenesis as evidenced by LOH at the MEN1 locus and resultant reduced menin staining.

MEN4

MEN4 (OMIM #610755) is a recently described syndrome with clinical features similar to MEN1 resulting from mutations in the CDKN1B gene.

Its identification stemmed from the observation of the spontaneous development of endocrine neoplasia occurring within the first year of life in a Sprague–Dawley rat colony (Fritz et al. 2002). This syndrome, termed MENX, consisted of bilateral phaeo, paraganglioma, parathyroid hyperplasia and pituitary adenomas preceded by juvenile cataracts. Despite the clear overlap in clinical features with both MEN1 and MEN2, no identified mutations in MEN1 or RET were identified and inheritance was autosomal recessive (Fritz et al. 2002). Subsequent work identified the causative gene to be Cdkn1b which encodes the cyclin-dependent kinase inhibitor p27Kip1 (Pellegata et al. 2006), a tumour suppressor previously implicated in pituitary tumorigenesis in knockout mice (Nakayama et al. 1996) and known to be downregulated in human pituitary adenomas (Lidhar et al. 1999, Korbonits et al. 2002). A pathogenic truncating mutation in the human orthologue CDKN1B was identified in a 48-year-old woman with a personal history of acromegaly and primary hyperparathyroidism and a family history of renal...
angiomyolipoma in a confirmed mutation carrier (Pellegrata et al. 2006). Subsequently, a number of cases of both functional (Georgitsi et al. 2007, Agarwal et al. 2009, Tichomirowa et al. 2012, Occhi et al. 2013, Sambugaro et al. 2015) and non-functional (Molatore et al. 2010) PAs have been reported in patients with germline mutations in CDKN1B, although they account for only a minority of MEN1 mutation negative patients (Ozawa et al. 2007, Igreja et al. 2009). Mutations in other cyclin-dependent kinase inhibitors have also been linked to MEN. Combined knockout of p18 and p27 in mice results in a similar MEN1/MEN2 overlap syndrome with development of PAs and phaeos in combination with parathyroid, thyroid C cell and pancreatic hyperplasia (Franklin et al. 2000). Agarwal et al. (2009) identified mutations in three other cyclin-dependent kinase inhibitor genes (p15, p18 and p21) in a large cohort of mutation-negative MEN1 patients, albeit with a low overall prevalence. None of these patients had a phaeo/PGL.

In spite of the very high prevalence of phaeo/PGL in these animal models – 95% for phaeo, 85% for PGL in MENX rats (Fritz et al. 2002), 91% for phaeo in double p18 and p27 knockout mice (Franklin et al. 2000) – no case of a phaeo or PGL has been reported in the context of MEN4 or a germline mutation in a cyclin-dependent kinase inhibitor gene in humans.

Aryl hydrocarbon receptor-interacting protein

Phaeo/PGL have not been reported in patients with mutations in AIP (Beckers et al. 2013, Hernández-Ramírez et al. 2015). No phaeo/PGL or mutations in phaeo/PGL-predisposing genes have been identified in 23 families with AIP mutation negative familial isolated pituitary adenomas (Dènes et al. 2015).

Mimics

When considering the coexistence of two rare diagnoses, Occam’s razor dictates that it is necessary to be aware of other pathologies that might masquerade as either a pituitary lesion or pituitary hyper-function.

Phaeo/PGL can rarely secrete pituitary hormones, such as ACTH, mimicking a functional PA, although a pituitary lesion is usually absent, unless an incidentaloma co-exists (Khalil et al. 1999, Yaylali et al. 2008). Ectopic hypothalamic hormone secretion, such as GHRH, by a phaeo/PGL is even rarer but constant trophic stimulation can result in pituitary hyperplasia (Roth et al. 1986) which could be interpreted as a PA and potentially lead to an unnecessary pituitary procedure (Vieira Neto et al. 2007).
Lesions within and around the sella can mimic PAs and might be coincidental, for example, Rathke’s cleft cyst in VHL (Huff et al. 2014), related to a particular syndrome, such as haemangioblastomas in VHL (Goto et al. 2001, Lonsor et al. 2009, Kanno et al. 2013), or the other pathology as in the case of an intrasellar PGL (Boari et al. 2006).

We summarise the genetic background of the published cases of coexisting PA and pheao/PGL in Figure 3 and show the potential mechanisms leading to the development of coexisting PA and pheao/PGL in Figure 4.

Summary

In conclusion, mutations in SDHA, SDHB, SDHD, MEN1 and probably SDHC have already been heavily implicated in the rare association of PA and pheao/PGL. Given the recent advances in this area it is likely that additional genetic culprits will be identified.

Declarations of interest

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

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