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

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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

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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 both pathologies occur in the same individual and many 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 *SDH*x 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 macroprolactinomas 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

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Table 1 Patients with pituitary adenoma and phaeochromocytoma/paraganglioma with identified genetic mutations

Patient no.	Sex	Pituitary				Phaeo/PGL			Family history	Mutation	Other info	Reference
		Type	Size	Treatment	Age	Type	Treatment	Age				
1	F	PRL	NK	NK	27	Phaeo	NK	NK	Nil	*SDHA* c.91C>T p.Arg31Ter, *VHL* c.589G>A p.Asp197Asn		Dénes *et al.* (2015)
2	M	GH	Macro	SSA	84	PGL	Nil	84	Nil	*SDHAF2* c.-52T>C	HNPGL	Dénes *et al.* (2015)
3	M	PRL	Macro	DA, surgery	33	PGL	Surgery	33	Mother: PRL, Brother: PGL	*SDHB* c.298T>C p.Ser100Pro	HNPGL PA: LOH at *SDHB* locus, intracyto-plasmic vacuoles	Dénes *et al.* (2015)
4	F	NFPA	Macro	Surgery x3, RT	53	PGL	RT	28	Sister: glioma	*SDHB* c.587G>A p.Cys196Tyr	HNPGL PA: LOH at *SDHB* locus, intracyto-plasmic granules	Dénes *et al.* (2015)
5	F	PRL	Macro	DA, RT	60	PGL	RT	60	Not known	*SDHB* c.423+1G>A	HNPGL	Dénes *et al.* (2015)
6	F	NFPA	Micro	Nil	50	Phaeo	Surgery	50	Not known	*SDHB* c.770dupT p.Asn258GlufsTer17	Adrenal cortical hyperplasia	Dénes *et al.* (2015)
7	M	GH	NK	SSA	72	PGL	Nil	70	Brother & niece: PA, sister: bilateral HNPGL	*SDHB* c.689G>A p.Arg230His	Bilateral HNPGL	Xekouki *et al.* (2015)
8	F	PRL	Micro	NK	50	PGL	NK	47	Brother: HNPGL, grandmother: GIST	*SDHB* c.642+1G>A, splice site alteration	Metastatic PGL GIST (age 38)	Xekouki *et al.* (2015)
9	M	PRL	Macro	DA	53	PGL	Surgery	38	Cousin: PA, Brother: PGL	*SDHC* c.380A>G p.His127Arg	HNPGL	Dénes *et al.* (2015)
10	F	PRL	Macro	NK	60	PGL	NK	60	Nil	*SDHC* c256-257insTTT pPhe85dup	HNPGL	López-Jiménez *et al.* (2008)
11	F	PRL	Macro	Surgery, DA	23	PGL	Surgery	32	Sister, aunt and grandmother: PA; sister bilateral HNPGL	*SDHD* c.242C>T, p.Pro81Leu	Bilateral HNPGL	Xekouki *et al.* (2015)
12	M	PRL	Macro	DA, surgery	60	PGL, Phaeo	Surgery (Phaeo)	62	NK	*SDHD* c.274G>T p.Asp92Tyr	HNPGL PA: LOH at *SDHD* locus, SDHB IHC negative, SDHA IHC positive	Papathomas *et al.* (2014)
13	F	GH	Macro	Surgery, SSA	56	PGL	NK	56	Father and 2 sisters: HNPGL; sister: GIST	*SDHD* c.274G>T p.Asp92Tyr	NHPGL PA: no LOH at *SDHD* locus, SDHA and SDHB IHC positive	Papathomas *et al.* (2014)

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Table 1 *Continued*

Patient no.	Sex	Pituitary				Phaeo/PGL			Family history	Mutation	Other info	Reference
		Type	Size	Treatment	Age	Type	Treatment	Age				
14	F	PRL	Macro	DA, surgery	33	PGL	Surgery x2	39	Aunt, uncle, brother HNPGL	*SDHD* c.242C>T p.Pro81Leu	Bilateral HNPGL	Varsavsky *et al.* (2013)
15	M	GH	Macro	SSA, surgery	37	PGL, Phaeo	Surgery	37	Uncle HNPGL	*SDHD* c.298_301del, premature stop at codon 133 *AIP* & *CDKN1B* polymorphism	HNPGL, abdo and pelvic PGL, bilateral Phaeo PA: LOH at *SDHD* locus, reduced SDHD protein	Xekouki *et al.* (2012)
16	M	GH/P-RL	Macro	Surgery, RT, DA	27	Phaeo	Surgery	31	Nil	*MEN1* c.1452delG p.Thr557Ter	HPTH, carcinoid Pheo: LOH at *MEN1* locus, negative menin staining	Dénes *et al.* (2015)
17	F	NK	Macro	NK	45	PGL	NK	45	Nil	*MEN1* c.196_200dupAG-CCC –> frameshift (pathogenic), polymorphism C423T –> no amino acid change	Abdominal PGL, breast cancer, adrenal adenoma, uterine leiomyoma, parathyroid adenomas, thymic carcinoid, lung hamatoma; raised IGF-1, prolactin, UFC	Jeong *et al.* (2014)
18	NK	PRL	NK	NK	NK	Phaeo	Surgery	48	NK	*MEN1* p.Lys119Ter *RET* WT	HPTH, pNET	Langer *et al.* (2002)
19	NK	NK	NK	NK	NK	Phaeo	NK	NK	NK	*MEN1* c.320del2	HPTH, pNET, adrenal adenoma	Dackiw *et al.* (1999)
20	M	GH	Macro	Surgery	62	Phaeo	Surgery	62	Nil	*RET* p.Cys618Ser	HPTH, MTC	Heinlen *et al.* (2011)
21	M	ACTH	Micro	Surgery x2	68	Phaeo	Surgery	66	Son: HPTH	*RET* c.1900T>C, p.Cys634Arg	Bilateral pheo HPTH, MTC	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, hyperparathyoidism; IGF-1, insulin-like growth factor 1; UFC, urinary free cortisol; NK, not known.

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Table 2 Patients with pituitary adenoma and phaeochromocytoma/paraganglioma without identified mutations but with suspicious features

Patient no.	Sex	Pituitary				Phaeo/PGL			Family history	Genetics tested	Other info	Reference
		Type	Size	Treatment	Age	Type	Treatment	Age				
1	F	GH	Macro	Surgery, RT, DA, SSA	56	Phaeo	Surgery	66	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*	GIST, thyroid follicular adenoma	Boguszewski *et al.* (2012), Dénes *et al.* (2015)
2	M	NFPA	Macro	Surgery	53	PGL	Surgery	50	Father: PA	*SDHA* c.969C>T p.Gly323Gly[a] *SDHB-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B* all normal	Abdominal PGL Wilms tumour, liposarcoma, renal oncocytoma; PA: no LOH at SDHA locus, intracytoplasmic vacuoles, SDHA and B staining preserved	Dénes *et al.* (2015)
3	F	ACTH	NK	NK	61	PGL	NK	61	Nil	*SDHA-D, MEN1, RET, AIP*	Bilateral HNPGL	Xekouki *et al.* (2015)
4	F	PRL	NK	NK	35	Phaeo	NK	55	Nil	*SDHA-D, MEN1, RET, AIP*	Bilateral phaeo	Xekouki *et al.* (2015)
5	F	PRL	Macro	NK	60	PGL	RT	60	Nil	*SDHB*	HNPGLs	Parghane *et al.* (2014)
6	F	PRL	Micro	DA	33	PGL	Surgery	43	Brain tumour	*SDHB* c.18C>A p.Ala6Ala[b] 3 PTEN polymorphisms	HNPGL PTC, features of Cowden syndrome	Efstathiadou *et al.* (2014)
7	M	GH	Macro	Surgery	29	Phaeo	Surgery	29	Nil	Nil	Bilateral phaeo Lipoma, metastatic PTC	Sisson *et al.* (2012)
8	NK	GH	NK	NK	NK	Phaeo	NK	NK	MEN1	Nil	Bilateral phaeo HPTH, pNET Clinical features NF1	Gatta-Cherifi *et al.* (2012)
9	M	GH	Macro	Surgery	45	PGL, Phaeo	Surgery x3	54	Father HNPGL, Sister: adrenal abnormality	Nil	Abdominal, HN, cardiac PGLs	Zhang *et al.* (2011)
10	M	NFPA	Micro	Nil	43	Phaeo	Surgery	43	Nil	*RET*	Lipoma, pectus excavatum, pleomorphic parotid adenoma. Acromegaly cured by adrenalectomy	Baughan *et al.* (2001)
11	M	GH	U	Surgery	20	Phaeo, PGL	Surgery	20	Nil	*RET*	Bilateral phaeo Abdominal PGL	Teh *et al.* (1996)
12	M	PRL	NK	NK	32	Phaeo	NK	32	MEN1	Nil	Malignant phaeo HPTH	Carty *et al.* (1998)
13	M	PRL	Macro	Surgery	26	Phaeo	NK	26	NK	Nil	HPTH, MTC	Bertrand *et al.* (1987)

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Table 2 *Continued*

Patient no.	Sex	Pituitary				Phaeo/PGL			Family history	Genetics tested	Other info	Reference
		Type	Size	Treatment	Age	Type	Treatment	Age				
14	F	NFPA	NK	NK	70	PGL	NK	70	Daughter and granddaughter: PA, bilateral HNPGL	Nil	Bilateral HNPGL HPTH, PTC, gastric leiomyoma, amyloidosis	Larraza-Hernandez *et al.* (1982)
15	F	GH	Macro	NK	U	Phaeo	NK	NK	NK	Nil	Malignant phaeo HPTH, elevated calcitonin	Anderson *et al.* (1981)
16	F	GH	Macro	NK	53	Phaeo	NK	53	NK	Nil	HPTH	Myers & Eversman (1981)
17	F	PRL	NK	NK	23	Phaeo	NK	23	NK	Nil	HPTH, gastrinoma, adrenal adenoma	Alberts *et al.* (1980)
18	F	GH	Macro	NK	15	Phaeo	NK	15	NK	Nil	HPTH	Manger & Glifford (1977)
19	F	Chrom	NK	NK	52	Phaeo	NK	52	NK	Nil	PTC	Melicow (1977)
20	F	GH	NK	NK	19	PGL	NK	19	NK	Nil	PGL (HN, pelvis) HPTH	Farhi *et al.* (1976)
21	F	GH	NK	NK	36	PGL	NK	36	NK	Nil	HNPGL HPTH, hyperplasia of antral and duodenal gastrin cells	Berg *et al.* (1976)
22	F	NFPA	NK	NK	43	Phaeo	NK	43	NK	Nil	HPTH, MTC	Wolf *et al.* (1972)
23	M	GH	NK	RT	51	Phaeo	Surgery	41	NK	Nil	Bilateral phaeo MTC, FH MEN1 for six generations	Steiner *et al.* (1968)

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, hyperparathyoidism; NK, not known; MEN1, multiple endocrine neoplasia type 1; NF1, neurofibromatosis type 1.

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

[b]Single nucleotide polymorphism with a minor allele frequency of 0.2% and a genotype frequency of 0.5% (Abecasis *et al.* 2012).

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Table 3 Patients with pituitary adenoma and phaeochromocytoma/paraganglioma without identified mutations or other suspicious features

Patient no.	Sex	Pituitary				Phaeo/PGL			Family history	Genetics tested	Other info	Reference
		Type	Size	Treatment	Age	Type	Treatment	Age				
1	F	GH	NK	NK	35	PGL	NK	58	Nil	*SDHA-D, MEN1, RET, AIP*	Bladder PGL	Xekouki *et al.* (2015)
2	F	NFPA	NK	NK	39	Phaeo	NK	34	Nil	*SDHA-D, MEN1, RET, AIP*		Xekouki *et al.* (2015)
3	F	GH	Macro	Surgery, RT, SSA	39	Phaeo	Surgery	20	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*		Dénes *et al.* (2015)
4	F	NFPA	Macro	Surgery, RT	73	PGL	RT	73	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*	HNPGL	Dénes *et al.* (2015)
5	M	GH	Macro	Infarcted	16	Phaeo	NK	16	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*		Dénes *et al.* (2015)
6	M	PRL	Macro	Surgery	40s	PGL	NK	52	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*	HNPGL	Dénes *et al.* (2015)
7	F	PRL	NK	NK	27	Phaeo	NK	41	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*		Dénes *et al.* (2015)
8	M	NK	NK	NK	NK	Phaeo/PGL	NK	NK	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*		Dénes *et al.* (2015)
9	F	PRL	Micro	DA	40	Phaeo	Surgery	38	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*		Dénes *et al.* (2015)
10	M	PRL	Micro	DA	56	Phaeo	Surgery	56	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*		Dénes *et al.* (2015)
11	F	PRL	Macro	DA	61	Phaeo	Surgery	61	Nil	*SDHA-D, AF2, MEN1, RET, AIP, VHL, TMEM127, MAX, FH, CDKN1B*		Dénes *et al.* (2015)
12	F	NFPA	Micro	Nil	52	Phaeo	Surgery	52	Nil	*SDHA-D, AF2, RET, MAX, TMEM127, VHL*	GHRH secreting Phaeo	Mumby *et al.* (2014)
13	M	NFPA	Micro	Nil	64	Phaeo	Surgery	64	Nil	Nil	Cushing's (cured post-adrenalectomy)	Yaylali *et al.* (2008)

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Table 3 *Continued*

Patient no.	Sex	Pituitary				Phaeo/PGL			Family history	Genetics tested	Other info	Reference
		Type	Size	Treatment	Age	Type	Treatment	Age				
14	M	NFPA	Macro	Surgery	59	Phaeo	Surgery	59	Nil	Nil		Breckenridge *et al.* (2003)
15	M	NFPA	Macro	Surgery	56	Phaeo	Nil	56	Nil	Nil		Dünser *et al.* (2002)
16	F	GH	Macro	Surgery	57	Phaeo	Surgery	57	Nil	Nil		Sleilati *et al.* (2002)
17	F	NFPA	Micro	Nil	44	Phaeo	Surgery	44	Nil	Nil	Cushing's (cured post-adrenalectomy)	Khalil *et al.* (1999)
18	M	PRL	Macro	Surgery	20	PGL	Surgery	20	NK	NK	HNPGL	Azzarelli *et al.* (1988)
19	F	PRL	Micro	NK	NK	Phaeo	NK	NK	NK	NK		Meyers (1982)
20	NK	NK	NK	NK	U	PGL	NK	NK	NK	Nil	HNPGL	Blumenkopf & Boekelheide (1982)
21	F	GH	NK	NK	NK	Phaeo	NK	NK	NK	Nil		Anderson *et al.* (1981)
22	F	NK	Macro	NK	22	Phaeo	NK	22	NK	Nil		Janson *et al.* (1978)
23	NK	GH	NK	NK	NK	Phaeo	NK	NK	NK	Nil		Kadowaki *et al.* (1976)
24	F	GH	NK	NK	U	Phaeo	NK	NK	NK	Nil		Miller & Wynn (1971)
25	F	GH	NK	NK	U	Phaeo	NK	NK	NK	Nil		O'Higgins *et al.* (1967)
26	M	GH	Macro	RT	23	Phaeo	Nil	41	NK	Nil		Kahn & Mullon (1964)
27	M	GH	NK	NK	U	Phaeo	NK	NK	NK	Nil		German & Flanigan (1964)
28	NK	GH	NK	NK	U	Phaeo	NK	NK	NK	Nil		Iversen (1952)

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.

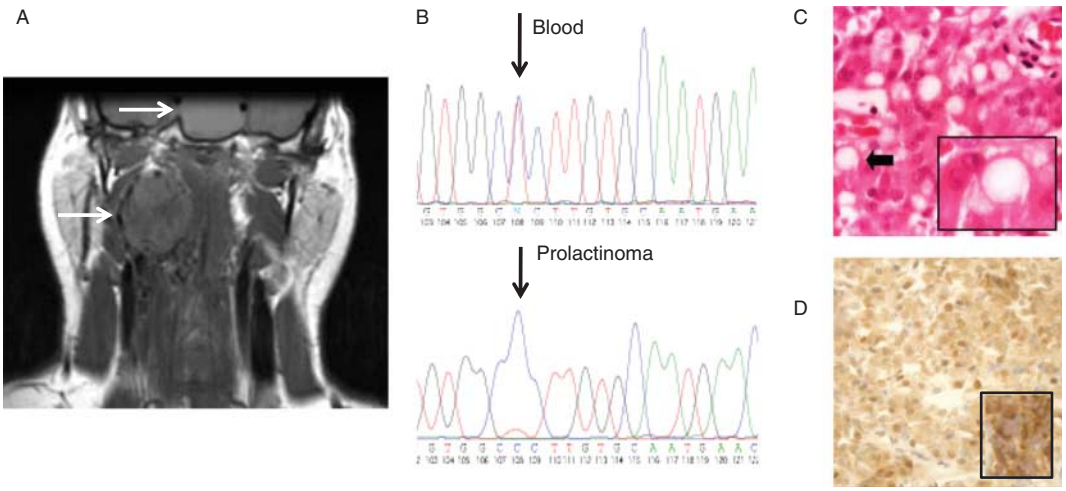

Figure 1

Clinico-pathological examples of coexistent PA and phaeo/PGL in a patient with an *SDHB* mutation. Magnetic resonance image (A) of a pituitary macroadenoma (upper arrow) and glomus vagale tumour (lower arrow) in a 33-year-old man with a germline *SDHB* mutation. He presented with visual loss due to the macroadenoma and pituitary imaging also revealed a mass arising in the carotid space. There is loss of heterozygosity (B) at the *SDHB* locus in a pituitary adenoma, which contains intracytoplasmic vacuoles (C; hematoxylin and eosin, ×40) and stains negative for SDHB (D; ×20, inset: positively staining paraganglioma). Reproduced, with permission, from Dénes J, Swords F, Rattenberry E, Stals K, Owens M, Cranston T, Xekouki P, Moran L, Kumar A, Wassif C, *et al.* 2015 Heterogeneous genetic background of the association of pheochromocytoma/paraganglioma and pituitary adenoma – results from a large patient cohort. *Journal of Clinical Endocrinology & Metabolism* **100** E531–E541. Published under the Creative Commons Attribution (CC BY) license.

of the six patients had PGL. An additional three patients with *SDHB* mutations with a PA but without a phaeo/PGL have been described (Benn *et al.* 2006, Dénes *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; Efstathiadou *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).

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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 phaeos. 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 α-subunits of HIF for degradation by the proteasome. When this does not occur, as is the case with mutant pVHL, HIFα heterodimerizes with HIFβ 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 in the tumour specimen (Dénes *et al*. 2015), although this is not an absolute requirement in VHL-related tumours (Banks *et al*. 2006). 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

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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 neutrophic 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 (Schnepp *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,

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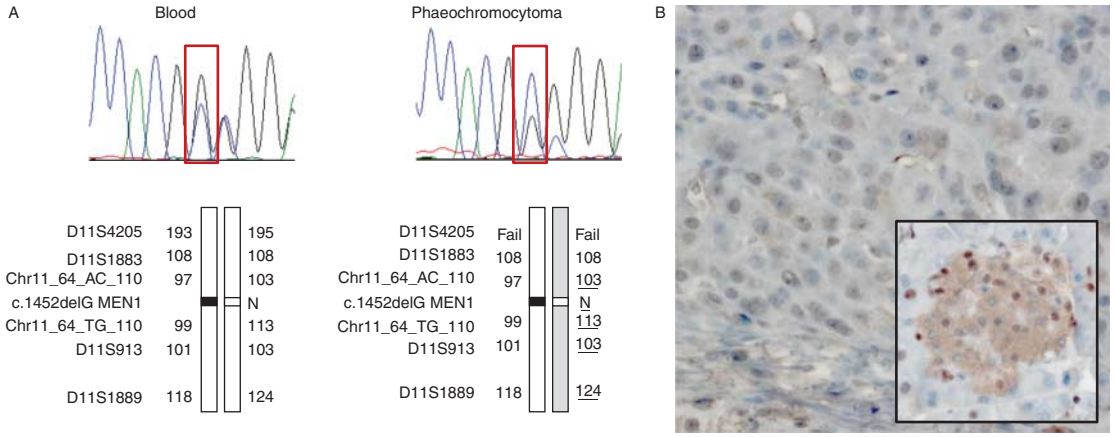

Figure 2

Clinico-pathological examples of coexistent PA and phaeo/PGL in a patient with an *MEN1* mutation. A 31-year-old man with an *MEN1* germline mutation c.1452delG and a history of a mixed growth hormone-prolactin secreting macroadenoma was diagnosed with a phaeochromocytoma. Analysis of the phaeochromocytoma demonstrated LOH at the *MEN1* locus (A) and absent menin staining (B; x20, inset: positively staining murine pancreatic islet). Reproduced, with permission, from Dénes J, Swords F, Rattenberry E, Stals K, Owens M, Cranston T, Xekouki P, Moran L, Kumar A, Wassif C, *et al*. 2015 Heterogeneous genetic background of the association of pheochromocytoma/paraganglioma and pituitary adenoma – results from a large patient cohort. *Journal of Clinical Endocrinology & Metabolism* **100** E531–E541. Published under the Creative Commons Attribution (CC BY) license.

Dénes *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; Dénes *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, Dénes *et al*. 2015). In one of these cases, LOH at the *MEN1* locus and weak menin staining was identified in the phaeo (Dénes *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 $p27^{Kip1}$ (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

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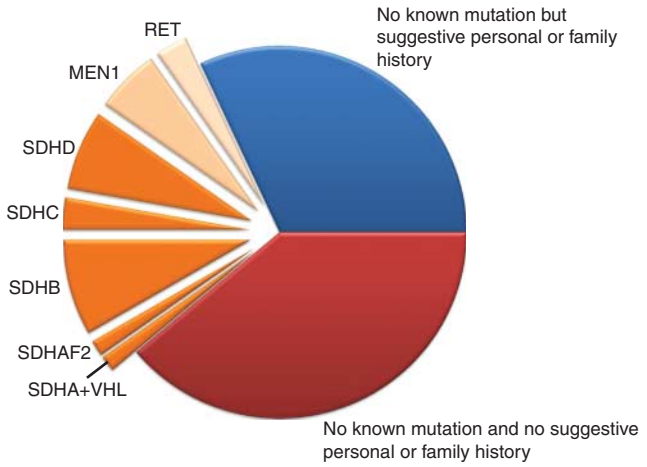

Figure 3
Summary of published cases of coexisting PA and phaeo/PGL. The details of 72 patients with coexisting PA and phaeo/PGL have been published. Twenty one patients (29%, Table 1) have either a confirmed genetic mutation in a recognised PA or phaeo/PGL-predisposing gene or a variant which is either thought to be pathogenic or has not been described as a polymorphism. Twenty three patients (32%, blue, Table 2) do not have a confirmed pathogenic genetic mutation in a PA or phaeo/PGL-predisposing gene but have features that are suggestive of a genetic link (family history of PA or phaeo/PGL, multifocal phaeo/PGL or associated endocrine pathology). Twenty eight (39%, red, Table 3) have arisen in patients without additional identified features.

angiomyolipoma in a confirmed mutation carrier (Pellegata *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 pheo/PGL or mutations in pheo/PGL-predisposing genes have been identified in 23 families with *AIP* mutation negative familial isolated pituitary adenomas (Dénes *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.

Pheo/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).

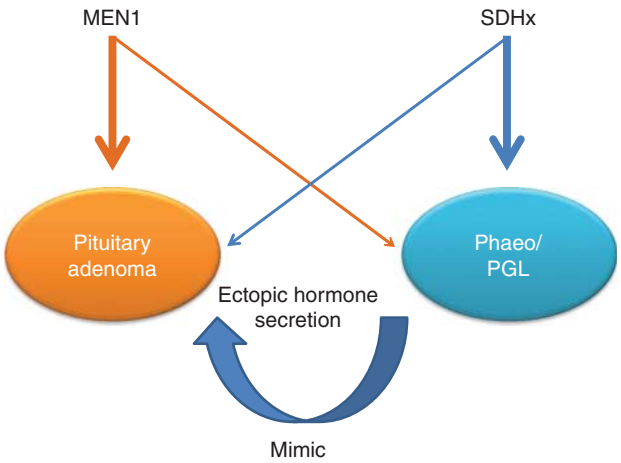

Figure 4
Schematic of potential mechanisms of the development of coexisting PA and phaeo/PGL. The development of PA and phaeo/PGL in the same individual may occur by coincidence or due to a shared pathogenesis. At present, there is evidence to suggest a role for both *SDHx* and *MEN1* mutations in the development of both these tumours. Ectopic secretion of hypothalamic or pituitary hormones by a phaeo/PGL may mimic a coexisting pituitary adenoma and should be a diagnostic consideration. More cases have been described in the literature of ectopic hormone secretion by a phaeo/PGL than by *bone fide* coexisting PA and phaeo/PGL.

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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, Lonser *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 phaeo/PGL in Figure 3 and show the potential mechanisms leading to the development of coexisting PA and phaeo/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 phaeo/PGL. Given the recent advances in this area it is likely that additional genetic culprits will be identified.

Declaration 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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