PHAEOCROMOCYTOMAS AND PARAGANGLIOMAS
An overview

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AES May 28th 2017
Arsenal defeat Chelsea to win FA Cup - watch live on BBC One
PLAN OF LECTURE

• Definitions and diagnosis
• Imaging techniques
• Germline disorders
• Management, including malignancy
• Genetic screening
DEFINITIONS

• **Phaeochromocytomas** are tumours arising from the adrenal medulla (c.0.1% of hypertensive population, 4% of adrenal incidentalomas)

• **Paragangliomas** are similar tumours arising from extra-adrenal sites, usually locations of sympathetic ganglia
  Prevalence 1/1700

• **Head-and-neck paragangliomas (HNPGLs)** arise from related tissue within the great arteries and veins in the neck: carotid body tumours, glomus jugulare etc – they are less often secretory
  Prevalence 1/4500
THE 10% RULE...?

• Generally true, but –

• The most important recent data have suggested that more than 30% of such tumours are likely to show germline mutations
  – VHL
  – MEN2
  – NF1
  – SDHx (A, B, C and D)
    • SDH-AP2, PH2, etc
  – TMEM127
  – MAX
BIOCHEMICAL DIAGNOSIS

• Urinary VMAs – no longer recommended
• Plasma catecholamines (70% sensitive)
• Urinary catecholamines (~90% sensitive)
• Urinary metanephrines (HPLC)
• Plasma metanephrines
  – Metanephrine, normetanephrine, 3-methoxytyramine
  – LC-MS, HPLC and EIA
BEWARE OF DRUG INTERFERENCE

- Plasma metanephrine 25,000 (N<500pmol/L)
- Urinary metanephrines normal
- Patient was taking midodrine for POTS

OCDEM and Leo Lam and colleagues, Auckland City Hospital
IMAGING DIAGNOSIS

• U/S of abdomen – not recommended
• CT
  – Use contrast and correct timing
• MRI
  – Useful for screening,
  – Bright T2 not invariant
• $^{123}$I-MIBG
• FDG-PET (very good for SDH-mutation positive)
• L-DOPA-PET best for head-and-neck paragangliomas
• $^{111}$In-octreotide good for malignant and HNPGL
CT SCANNING

• Should include triple-phase contrast

• No need for adrenoceptor blockade with non-ionic contrast media (Mukherjee et al 1997)

• Highly sensitive and specific
MRI

- High signal on T2 (but not all)
- Slightly worse resolution cf. CT
- Good for surveillance
123I-MIBG SCANNING

- 76 patients studies with 123I-MIBG and cross-sectional imaging

- **Sensitivity 75%**
  - 85% for phaeochromocytomas
  - 58% for paragangliomas
  - Negative scans correlated with small size and necrosis/haemorrhage
  - Unrelated to secretory status
  - Useful if considering 131I-MIBG therapy

(Bhatia et al 2008)
$^{123}$I-MIBG: SPECT imaging
LARGE PHAEOCHROMOCYCTOMA WITH CYSTIC/NECROTIC AREA

(Bhatia et al 2008)
RETROPERITONEAL PARAGANGLIOMA WITH POSITIVE MIBG UPTAKE

(Bhatia et al 2008)
PARAGANGLIOMA AS SHOWN BY DOPA-PET (left) AND MRI (right)

(Neumann et al. 2005)
RADIONUCLIDE IMAGING IN HEAD-AND-NECK PARAGANGLIOMAS

- 20 patients
- $^{68}$Ga-Dotatate vs $^{18}$F-DOPA vs $^{18}$FDG PET
- $^{18}$F-DOPA PET identified 38 lesions
- $^{18}$FDG PET identified 24/38
- $^{68}$Ga-Dotatate PET identified 38 +7

CONCLUSIONS: $^{68}$Ga-Dotatate PET is the preferred imaging modality for HNPGGLs

(Janssen et al 2016)
RADIONUCLIDE IMAGING IN PARAGANGLIOMAS

- 23 patients with phaeos and PGLs
- $^{68}$Ga-Dotatate vs $^{18}$FDG PET
- $^{18}$FDG-PET identified 91%
- $^{68}$Ga-Dotatate-PET identified 96% (SUV++)
- $(^{123}$MIBG 30%)

CONCLUSIONS: $^{68}$Ga-Dotatate PET is the preferred imaging modality for PGLs

(Chang et al 2016)
CONCLUSIONS: FUNCTIONAL IMAGING OF PARAGANGLIOMAS

\(^{18}\text{F-} \text{DOPA-PET/CT}\) is the imaging modality of choice where available.

\(^{68}\text{Ga-Dotatate PET/CT}\) is an excellent alternative, \(^{18}\text{FDG-PET}\) useful as a screen.

\(^{123}\text{I-} \text{MIBG}\) of limited value except when considering \(^{131}\text{I-} \text{MIBG}\) therapy.
Among 271 patients who presented with non-syndromic phaeochromocytoma and without a family history of the disease, 66 (24 percent) were found to have mutations. Of these 66, 30 had mutations of VHL, 13 of RET, 11 of SDHD, and 12 of SDHB. Younger age, multifocal tumors, and extra-adrenal tumours were significantly associated with the presence of a mutation.

24% overall

- VHL 11%
- RET 5%
- SDHD 4%
- SDHB 4%

(Neumann et al. NEJM 2002)
HIF-α signalling in hereditary PHAEO/PGL

Cluster 1

Cluster 2

[Image of diagram showing metabolic pathways and signaling molecules]
MICROARRAY CLUSTER ANALYSIS OF PHAEOCHROMOCYTOMAS

- Divide into two groups
  - SDHx and VHL: HIF-1α related
  - NF1 and MEN2 – membrane receptor related

» Patricia Dahia and colleagues 2005
Von HIPPEL-LINDAU DISEASE

- Autosomal dominant
- Clinical features
  - Cerebellar haemangioblastomas
  - Retinal angiomas
  - Renal cell carcinomas
  - Pancreatic tumours
  - Endolymphatic duct abnormalities
- Molecular biology
  - VHL protein targets HIF1α for degradation
- Nature of mutation affects phaeochromocytoma incidence
PHAEOCHROMOCYTOMAS IN VHL

- **Adrenal** (ie, not paragangliomas)
- **Bilateral**
- Usually noradrenaline secreting
- Related to mutations of non-critical regions
- Rarely malignant (5%)
PHAEOCHROMOCYTOMAS IN MEN2

• Around 50% of carriers

• Adrenal

• Adrenaline secreting

• Often bilateral

• Almost always benign
PHAEOCHROMOCYTOMAS IN NF1

- Only ~1% of NF1, but NF1 is a common disorder
- NF1 is a huge gene so not screened for unless known mutation
- NF1 acts on growth factor/MAPK/Akt pathway

- Usually unilateral and benign

- Other tumours: GIST, duodenal and islet NETs
PARAGANGLIOMA IN A PATIENT WITH NF1
TMEM-127

• Recently described by Patricia Dahia and colleagues

• Usually phaeochromocytomas, mean age 41.5 years

• Part of mTOR pathway

• Of 1000 ‘sporadic’ tumours screened, present in ~2% germline cells (Yao et al JAMA 2010)

• 50% bilateral, not reported as malignant (Toledo et al 2015)
MAX

• 1% of phaeochromocytomas/PGLs

• 50% bilateral, often with family history

• 10% malignant

• Maternal imprinting

(Burnichon et al 2012)
Role of Hypoxia-Inducible Factor α (HIF-α) under Normoxic and Hypoxic Conditions.
THE SDH FAMILY OF MUTATIONS

• Blockade of Krebs cycle leads to accumulation of succinate, which inhibits proline hydroxylase

• HIF1α which is not hydroxylated is not amenable to degradation

• HIF1α accumulates leading to proliferation and angiogenesis
THE SDH FAMILY OF MUTATIONS

- **SDH-A**: Leigh syndrome (phaeos very rare)
- **SDH-B**: Paragangliomas, often malignant
- **SDH-C**: HNPGLs, rare
- **SDH-D**: HNPGLs, occasional paragangliomas, male inheritance
- **SDH-AP2**: Two families of HNPGLs
- **PH2**: Paragangliomas associated with erythrocytosis
THE KREBS CYCLE

Pyruvic acid (3-C) → NAD⁺
→ Oxaloacetate (4-C)
→ malate (4-C) → NADH
→ fumarate → H₂O
→ succinate (4-C) → FADH₂
→ succinyl-CoA (4-C) → ATP
→ succinyl-CoA (4-C) → CoA
→ citrate → CoA
→ citrate (6-C) → H₂O
→ cis-aconitate → H₂O
→ isocitrate (6-C) → NAD⁺
→ isocitric dehydrogenase → Mn²⁺
→ oxalo-succinate (6-C) → NADH
→ α-ketoglutarate (5-C) → CO₂
→ α-ketoglutarate dehydrogenase complex (Mg²⁺ TPP, Lipoic acid, Transacetylase)
THE SDH COMPLEX
UNILATERAL PHAEOCHROMOCYTOMA IN A PATIENT WITH A MUTATION OF SDH-D
SDH-B MUTATIONS

• High penetrance (~80% by 80 years)

• Some 30% of all patients with malignant catecholamine-related tumours

• At least 30% malignant
OTHER SDH MUTATIONS

• SDH-AH2
  – Very rare

• SDH-C
  – Rare, usually HNPGLs

• SDH-D
  – HNPGLs, maternal imprinting, occasionally malignant
SDH-AF2 (SDH-5)

• Accessory factor for SDH-A, flavine adenine dinucleotide co-factor

• Very rare germline mutation

• Two families
  – One Spanish, one Dutch (unrelated)
  – HNPGLs

(Hao et al 2008, Bayley et al 2010)
CONCLUSIONS: Genetic testing for germline mutations in \textit{SDHX} should be considered in patients with the constellation of phaeo/PGLs and pituitary adenomas.
CASE REPORT: A 42 year-old male, with a family history of phaeo and PGL, was diagnosed as a carrier of the SDH-B mutation. He was also diagnosed with a macroprolactinoma and treated with cabergoline.

This case represents the ninth patient with an SDHB-associated pituitary adenoma.

A contrast CT chest scan, performed as part of the surveillance program for SDHB-associated tumours, revealed a small right lung lesion, which was found to be OctreoScan positive.

Two typical carcinoids (TCs) were found (according to the WHO 2015 classification)

Ki-67: 1% and 5% respectively

Immunohistochemistry: chromogranin A and synaptophysin positive
THE KREBS CYCLE

Fumarate is an oncometabolite
FH

- 598 patients without known germline mutations
- 5 germline mutations in FH, with LOH in tumour
- Malignant and multiple (Castro-Vega et al 2014)

- One childhood phaeo, 1/71 patients (Clark et al 2014)
MECHANISM OF FH ONCOGENICITY

Fumarate accumulation

TET

Demethylation

Mir-200ba429

Epithelial-to-mesenchymal transition

(Sciacovelli et al, Nature September 2016)
MRI OF MYOCARDIAL FUNCTION IN PHAEOCHROMOCYTOMAS

• Patients with phaeos pre- and post-surgery 29
• Patents cured 31
• Controls 14
• Hypertensive patients 51

• 1.5T MR
• LGE
• Native T1-mapping

Ferreira et al. 2016
CMR cardiac characterisation in phaeochromocytoma

Cine:
Structure, Function

Tagged CMR:
myocardial Strain

LGE:
Scar, Focal fibrosis

T1-mapping

Ferreira et al. 2016
Phaeochroocytoma vs. HTN vs. Normal

CMR

<table>
<thead>
<tr>
<th>Normal</th>
<th>HTN</th>
<th>Pheo (new)</th>
<th>Pheo (cured)</th>
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<tr>
<td><img src="image1.png" alt="Colored T1-map" /></td>
<td><img src="image2.png" alt="Colored T1-map" /></td>
<td><img src="image3.png" alt="Colored T1-map" /></td>
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<td><img src="image6.png" alt="Threshold T1-map" /></td>
<td><img src="image7.png" alt="Threshold T1-map" /></td>
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<td><img src="image11.png" alt="LGE" /></td>
<td><img src="image12.png" alt="LGE" /></td>
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</table>
Systolic dysfunction as detected by impaired myocardial strain on tagged CMR

Ferreira et al 2016
Diastolic dysfunction as detected by impaired myocardial strain on tagged CMR

Ferreira et al. 2016
Catecholamine myocarditis and left-ventricular involvement as detected by native T1-mapping

Ferreira et al. 2016
CONCLUSIONS ON CARDIAC FUNCTION

- Cardiac dysfunction common including myocarditis, systolic and diastolic dysfunction and focal fibrosis

- Distinct catecholamine ‘signature’

- Improvement in some parameters, but not all, especially diffuse and focal fibrosis
MANAGEMENT OF PHAEOCHROMOCYTOMA AND PARAGANGLIOMA

- $\alpha$-adrenoceptor blockade

- Phenoxybenzamine 10mg tds, increased to normalise BP to a usual dose of 1mg/kg
  - Postural hypotension, dizziness, nasal stuffiness, absent ejaculation

- Add $\beta$-blocker if required for tachycardia after 3-4 days

- Allow volume equilibration over 7-10 days
MANAGEMENT OF PHAEOCHROMOCYTOMA AND PARAGANGLIOMA

• Features suggesting malignancy
  – Paragangliomas > Phaeochromocytomas
  – Size (>5cm)
HOW COMMON IS MALIGNANCY, AND WHAT ARE THE IMPORTANT FACTORS?

- MD Anderson, 371 patients
- Phaeos and PGLs, 25% malignant
- Paragangliomas 60% malignant
- Size matters!
- Most important factor is PGL versus phaeo, especially mediastinum and abdomen
- Shorter survival with PGLs

(Ayala-Ramirez et al 2011)
MANAGEMENT OF MALIGNANT PHAEOCHROMOCYTOMA AND PARAGANGLIOMA

• ~30% have SDH-B germline mutations, occasionally VHL

• $^{131}$I-MIBG therapy where $^{123}$I-mIBG scan shows therapeutic uptake

• Standard chemotherapy is CVD: not very effective

• Case studies with sunitinib look promising
RADIOLABELLED $^{123}$I-MIBG SCAN
MIBG – METASTATIC PHAEOCHROMOCYTOMA
EFFECTS OF CHEMOTHERAPY

• Classical data suggested best combination was cyclophosphamide, vincristine and dacarbazine (CVD)
• NIH data suggested good long-term survival

• 25 patients
  – 16 received CVD, 9 did not

• Survival curves showed worse survival for CVD treatment (Nomura et al 2009)
TEMOZOLOMIDE IN NETs

29 PATIENTS WITH METASTATIC NETs plus malignant phaeochromocytomas

Temozolomide 150mg/m² for 7 days on alternate weeks
Thalidomide 50-400mg (100mg) daily

Biochemical response rate 40% (30% in phaeos)

Survival 79% 1y, 61% 2y

S/E lymphopaenia and opportunistic infections

(Kulke et al 2006)

60 year old female, marked clinical response to temozolomide – Bravo et al 2009
USE OF SUNITINIB IN MALIGNANT PARAGANGLIOMA

• Case reports on use of sunitinib in patients renal cell carcinoma
• 3 patients sunitinib 50mg od 4w, 2w off
• One complete response, 2 partial responses
  – Renal mass, response but then progression, VHL
  – Bladder PGL, SDH-B, near complete response of metastases at 40w
  – Malignant phaeo with metastases, regression by 3 months, well at 40w
• On-going trial

Joshua et al, JCEM 2009
USE OF SUNITINIB IN MALIGNANT PARAGANGLIOMA

• Consecutive series from M.D. Anderson, Houston, USA
• 17 patients,
  – 8/17 showed benefit by RECIST
  – 7/8 with SDH-B mutations responded
  – 4 showed fall in FDG-PET of bone metastases
  – 6/14 became normotensive
  – Progression free survival 4.1m
• Side-effects included hypertension, hand-foot syndrome, diarrhoea and fatigue
• Excellent response to combination of rapamycin and sunitinib

Ayala-Ramirez et al 2012
PFS in patients with progressive metastatic PHAEO or SPGL treated with sunitinib

Ayala-Ramirez et al 2012
BONE METASTASES IN MALIGNANT PHAEOCHROMOCYTOMAS

- 128 patients with malignant phaeochromocytomas and PGLs
- 71% with bone metastases, 20% exclusively in skeleton
- Presentation with severe pain
- Survival
  - Only bone mets 12y
  - Non-bone mets 7.5y
  - Both 5y

Ayala-Ramirez et al JCEM 2013
MALIGNANT PHAEOCHROMOCYTOPHATS

- Retrospective survey of 132 patients
- SDH-B mutations in 55%, worse survival
- 84% larger than 4.5cm
- Most had a noradrenergic phenotype

(Turkova et al 2016)
CONCLUSION

• Malignant phaeos/PGLs may be treated with $^{131}$I-MIBG, chemotherapy or sunitinib, but overall survival remains poor

• Is there an alternative approach...?
PI3K/Akt and MAPK/ERK pathways operate in parallel
USE OF EVEROLIMUS IN MALIGNANT PARAGANGLIOMA

- Four patients (London, Jerusalem) with progressive PGLs/phaeos resistant to all standard therapy

- Everolimus 10mg daily

- All progressed and succumbed

Druce et al HMR 2009
USE OF EVEROLIMUS IN MALIGNANT PARAGANGLIOMA

- Seven patients (South Korea) with progressive PGLs/phaeos resistant to all standard therapy

- Everolimus 10mg daily

- 5/7 showed stable disease, PFS 3.8months All progressed and succumbed

Oh et al Cancer 2012
NVP-BEZ235

RTKs: IGF-R, VEGF-R, EGF-R, RET

PI3K/Akt

ERK1/2

mTORC1

viability

Nölting et al JME 2012
NVP-BEZ235 plusLovastatin

RTKs: IGF-R, VEGF-R, EGF-R, RET

PI3K/Akt

ERK1/2

mTORC1

viability

Nölting et al JME 2012
Cell viability in MPC (A) and MTT (B) cells: MPC and MTT cells were pre-treated with lovastatin for 24h before everolimus was added, and the combination of both drugs was incubated for 48h.

http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0143830
Combination of Lovastatin with NVP-BEZ235

MPC Cell viability curves

Nölting et al. JME 2012
Lovastatin alone and in combination with 13-cis-retinoic acid in allograft phaeochromocytoma (MTT cell) nude mice

Nölting et al., Endocrinology, 2014
CONCLUSION

• In animal models (cell lines and allografts) combination therapies with specific targeted agents are more effective than single targeted agents

• Some drugs can be re-purposed
MANAGEMENT OF MALIGNANT PHAEOCHROMOCYTOMA AND PARAGANGLIOMA

• ~30% have SDH-B germline mutations, occasionally VHL/MAX

• $^{131}$I-mIBG therapy where $^{123}$I-mIBG scan shows therapeutic uptake

• Standard chemotherapy is CVD, for non-response or relapse try temozolomide

• Sunitinib may induce short-term remission

• **Combination therapy with targeted agents is probably the future**
CASE STUDY 1

• 45 year old lady, lives in Bristol
• History of multiple paragangliomas

• Presented to our endocrine clinic with:
  - Weight loss,
  - Frequent attacks of facial flushing, headache, sweating and hypertension, with a systolic blood pressure reaching 210 mmHg systolic
  - These episodes tended to occur approximately twice per month, and were precipitated by exercise or stress.
  - In contrast, she was also assessed on different occasions in which the attacks were said to be characterised by hypotension and dizziness
Family history

- Mother died at the age of 57 of multiple paragangliomas.

- Two brothers appeared to be unaffected.

- Her only child, a son aged 23 years, developed severe visual loss in 2013 and was diagnosed with a macroprolactinoma that had apparently responded to medical therapy.

- Confirmed SDH-C mutation
Investigations

• **Urine:**

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<th>Test</th>
<th>Result</th>
<th>Units</th>
<th>Range</th>
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<tr>
<td>NORMETADRENALIN</td>
<td>0.96</td>
<td>umol/24Hr</td>
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<tr>
<td>METADRENALINE</td>
<td>0.39</td>
<td>umol/24Hr</td>
<td>0.00-1.40</td>
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<td>3METHOXYTYRAMIN</td>
<td>9.23</td>
<td>umol/24Hr</td>
<td>* 0.00-2.55</td>
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<td>U. CREATININE</td>
<td>6.2</td>
<td>mmol/L</td>
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<td>URINE VOLUME</td>
<td>1.50</td>
<td>L</td>
<td></td>
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<tr>
<td>URINE PERIOD</td>
<td>23.40</td>
<td>Hours</td>
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• **Plasma:**

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<tr>
<td>NORMETANEPHRINE</td>
<td>191</td>
<td>pmol/L</td>
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<tr>
<td>METANEPHRINE</td>
<td>143</td>
<td>pmol/L</td>
<td>80-510</td>
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$^{18}$FDG-PET OF SDH-C ASSOCIATED PERICARDIAL PGL
MRI OF PERICARDIAL PARAGANGLIOMA

(Guelho et al 2015)
Medical Management

• High levels of methoxytyramine suggested that the tumour was dopamine-secreting

• As dopamine-receptor blockade can precipitate a catecholamine crisis in patients with excess noradrenaline or adrenaline release, she was started on $\alpha$-adrenoceptor blockade (doxazosin). She was then initiated on domperidone 10mg tds.

• She developed a sinus tachycardia, and so atenolol 50mg was added: surgery abandoned due to coronary arteries running through tumour
CASE STUDY 2

• 23y, PIH and stillbirth  Barts
• Left phaeochromocytoma
• Multiple paragangliomas
• Whipple’s for ?islet cell or duodenal tumour
• More paragangliomas removed

• Rectal carcinoma  Oxford
• 3 courses of $^{131}$I-MIBG in 2013
• Germline testing for all genes negative
HIF-2α

- Similar functions to HIF-1α
- Forms heterodimer with HIF-1β
  - Increases Cyclin D, VEGF, TGFα
  - Increases erythropoiesis vis EPO
  - Cell migration
  - Matrix remodelling
  - Iron absorption
  - Vascular invasion
# Initial 2 NIH patients: Clinical characteristics & laboratory values

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<th>Patient 1</th>
<th>Patient 2</th>
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<td><strong>Polycythaemia</strong></td>
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<tr>
<td><em>Red cheeks/lips</em></td>
<td>At birth</td>
<td>At birth</td>
<td>NA</td>
</tr>
<tr>
<td><em>Blue feet</em></td>
<td>8 yr</td>
<td>&lt; 1 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Erythrocytes</strong></td>
<td>7,780.000</td>
<td>7,850.000</td>
<td>5,220.000</td>
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<td><strong>Haematocrit</strong></td>
<td>50.5</td>
<td>59.3</td>
<td>44.9</td>
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<td><strong>Erythropoietin</strong></td>
<td>150</td>
<td>180</td>
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<td><strong>Multiple PGLs</strong></td>
<td>14 yr</td>
<td>18 yr</td>
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<td><em>Normetanephrine</em></td>
<td>4,834</td>
<td>858</td>
<td>112</td>
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<td><strong>Multiple SOMs</strong></td>
<td>29 yr</td>
<td>24 yr</td>
<td>-</td>
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SOM: somatostatinoma; URL: upper reference limit
Somatic gain-of-function HIF-2α (HIF2A) mutation

HIF-2α IHC

N: normal adrenal medulla

Pt. 1. A530T
Pt. 2. A530V

HIF-1α IHC

HIF-2α IHC

IHC

Blood

Tumor 1

Tumor 2

(PGL) (S)

Brief Report

Somatic HIF2A Gain-of-Function Mutations in Paraganglioma with Polycythemia

Zhengping Zhuang, M.D., Ph.D., Chunzhang Yang, Ph.D.,
Felipe Lorenzo, M.D., Ph.D., Maria Morino, M.D., Tito Fojo, M.D., Ph.D.,
Electron Kebebew, M.D., Ven Popovic, M.D., Ph.D.,
Christopher A. Stanski, M.D., D.Sc., Joseph F. Reddy, M.D.
Gain-of-function somatic *HIF2A* mutation and its consequences

Only 9.1% and 16.7% of the mutated HIF-2α were hydroxylated respectively.

HIF-2α: half-life increased from 14.4 min to 57.6 and 79.8 min.

Only about 20% of the VHL protein bound to the mutant HIF-2α.
CASE STUDY 2

- Multiple paragangliomas
- Many removed, some treated with MIBG
- Germline testing for all genes negative
- Then revealed childhood history of polycythaemia...
- Germline testing of HIF-2α normal
- Somatic mutation of HIF-2α c. C82860T, p. A530V
HIF-2α

- Somatic gain of function mutations in two patients: paraganglioma/phaeochromocytoma, somatostatinoma, polycythaemia (Zhuang et al 2012)

- Possible mosaicism
GENETIC SCREENING?

GERMLINE MUTATIONS IN TRULY ‘SPORADIC’ PHAEOCHROMOCYTOMAS

• Meta-search of 31 studies
  – No family history
  – No syndromic features
  – Unilateral
  – No metastases

• 10 genes surveyed

• 11-13% positive germline mutations (SDH-B 5%) (Brito et al 2015)
GERMLINE MUTATIONS IN TRULY ‘SPORADIC’ PHAEOCHROMOCYTOMAS

• Analysis of Oxford patients using a 10-gene panel
• 25% showed germline mutations
  – 12% VHL
  – 7% MEN2/3
  – 3% SDH
  – 2% MAX
  – 1% TMEM127

• 15% in non-syndromic unilateral phaeochromocytomas
• More common in young patients and those with malignant and bilateral tumours

(Sbardella et al 2017)
CONCLUSIONS: GENETICS

Approaching 50% of all phaeochromocytomas and paragangliomas will be found to have a germline mutation or mosaicism.

Many of the SDH syndromes may have associated other tumours such as renal cell carcinoma, pituitary tumours, lung carcinoids and possibly other tumours (rectal CA?)
SUGGESTED GUIDELINES FOR HNPGLs 1  
(Based on experience in Oxford)

- All patients with phaeochromocytomas and paragangliomas should have extensive germline genetic testing.
- Positive testing will determine follow-up and screening.
- First-degree relatives should be offered genetic screening.
SUGGESTED GUIDELINES 2

• For patients and carrier mutation-positive:
  – At baseline, assess plasma or urinary metanephrines
  
  – *Perform* $^{18}$FDG-PET/CT scan

  – Neck-to-pelvis MRI

(For SDH-positive relatives with PGLs, 13% +ive for tumours; Raygada et al 2014)
SUGGESTED GUIDELINES 3

- For all patients with previous tumour, review clinically every 6 months with assessment of metanephrines; for asymptomatic carriers, screen every 12 months

- Repeat abdominal MRI annually

- Repeat neck-to-pelvis MRI every 2-3 years
SUGGESTED GUIDELINES 4

• The rationale for surgery of head-and-neck PGLs is removal of malignancy, functionality, or cosmetic growth

• Surgery of HNPGLs can be associated with significant morbidity

• Consider radiotherapy/radiosurgery when appropriate
SUGGESTED GUIDELINES 5

• Age to consider screening uncertain: suggest age 5y clinically and with urinary metanephrines, ultrasound annually from 10y

• For SDH-B/MAX/FH as above but with annual MRI from age 10y

• For all others, adult screening programme from 16y
SUGGESTED GUIDELINES 6

• Functional imaging can add information for identifying PGLs and HNPGLs

• $^{18}$FDG-PET/CT a useful screening technique, especially for SDHx mutations

• $^{68}$Ga-Dotatate-PET/CT likely to become the imaging investigation of choice, and has therapeutic implications
MALIGNANT PHAEOCHROMOCYCTOMAS AND PGLs

- Only surgery is curative
- Radiolabelled MIBG and ?octreotide when scan positive
- Conventional chemotherapy with CVD, but not clear if it extends survival; consider temozolomide
- Targetted agents, ie, sunitinib
International Symposium on Phaeochromocytoma and Paraganglioma 2017
30 Aug - 3 Sep 2017

Oral Submission and Earlybird Registration deadline EXTENDED until June 2 for ESA Members

Sofitel Sydney Wentworth

www.isp2017.org
### NEW ASSOCIATION for SDH?
COMBINATION PHEO/PGL AND PITUITARY ADENOMA

#### First description
- 1952

<table>
<thead>
<tr>
<th>Subgroups of pituitary adenoma + pheo/PGL cases</th>
<th>Number of the cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHRH secreting pheochromocytoma</td>
<td>4</td>
</tr>
<tr>
<td>CRH secreting pheochromocytoma</td>
<td>4</td>
</tr>
<tr>
<td>Pituitary adenoma + pheo/PGL</td>
<td>44</td>
</tr>
<tr>
<td>Pheo/PGL + pituitary adenoma in the family (not in the same individual)</td>
<td>4</td>
</tr>
<tr>
<td>Hereditary pheo syndrome (without pheo/PGL) + pituitary adenoma</td>
<td>9</td>
</tr>
<tr>
<td>Hereditary pituitary syndrome (without pituitary disease in patient) + pheo/PGL</td>
<td>4</td>
</tr>
<tr>
<td>Digenic (?)</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOGETHER</strong></td>
<td><strong>70</strong></td>
</tr>
</tbody>
</table>

Prevalence in the general population of:

- symptomatic pituitary adenomas 1:1063 to 1:1282
- clinically diagnosed pheo/PGL 1:2500 to 1:6667

Common pathogenic mechanism? 
Coincidence? 

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*39 M. Korbonits et al 2015*
I-MIBG SCANNING

- 76 patients studied with $^{123}$I-MIBG and cross-sectional imaging

- Sensitivity 75%
  - 85% for phaeochromocytomas
  - 58% for paragangliomas
  - Negative scans correlated with small size and necrosis/haemorrhage
  - Unrelated to secretory status
  - Useful if considering $^{131}$I-MIBG therapy

(Bhatia et al 2008)
Background

• **1986** (19 years of age): Left glomus jugulare tumour, removed surgically, residual multiple neurological defects.
• **1990**: Relapse, requiring a second operation.
• **1997**: Gamma-knife treatment to the surgical bed of the tumour.
• **2003**: Mass in the right side of her neck which was confirmed to be a carotid body tumour on removal.
• **2004**: Paraganglioma was found within her thyroid, which was only partially removed, but then she underwent a total thyroidectomy with complete removal of the paraganglioma a year later.
• **2006**: $^{18}$FDG-PET scan showed two paragangliomas in her right lung that were removed surgically.
• **2011**: Recurrence of her right carotid body tumour that was treated by external beam radiotherapy (45 Gy).

• All of these tumours had been reported to be non-secretory.
Polycythaemia and Paraganglioma

PHAEO/PGL & polycythaemia

PHD: prolyl hydroxylase
pVHL: von Hippel-Lindau protein

Ladroue et al. NEJM 2008; 359:2685
Lee et al. Annu. Rev. Pathol. 2011; 6:155
Jochmanova et al. JNCI 2013; 105:1270
Genes targeted by HIF upregulation

HIF-α

- Invasion
  - E-MET, ET1, FN1, MMP2, MMP14, PLAU

- Cell proliferation//differentiation/survival
  - HK1, HK2, IG2, IGFBP1, IGFBP3, BIRC5, TGFe, TGFβ3, PDGFB, WSB1, ID2, P21, MERTK, F355P, Mip3, CDyn G2, DEC1, Oct4, NOTCH1

- Glucose/energy metabolism
  - GPI, GLUT1, GLUT3, HK1, HK2, LDHA, PKD1, PKM2, ACO, ALDOA, ALDDE, GAPDH5, PFKL, PGK1

- Genomic instability
  - DEC1, MSH2, MSH6, NBS1

- Angiogenesis
  - VEGF, ANGPT2, KITLG, PDGF, PDGFB, PIGF, SDF1, ID2, AM, ET1, HO-1, VEGFR1, NOS2, a1B-adrenergic receptor

- pH regulation
  - CA9, CA12

- Metastasis
  - ANG1, CXC4, LOX, SDF1

- Epithelial-mesenchymal transition
  - SNAI4, SIP, TWIST1, ZEB2, ZEB2

- Red blood cell production and iron metabolism
  - Epo, TF, TFR, CP
Somatostatinoma: Definition/Background

SOMs are neuroendocrine (enterochromaffin cell) tumours characterised by somatostatin synthesis and release.

Somatostatinoma syndrome
- Diabetes
- Cholelithiasis
- Diarrhoea

Localisation
- Duodenum (2nd portion; NF1, MEN1)
- Pancreas (head; NF1, MEN1)
- Bile ducts, ovaries

Gall bladder
Common bile duct
Pancreas
Pancreatic duct
Duodenum

NF1: neurofibromatosis type 1; MEN1: multiple endocrine neoplasia type 1

Kloppel G., personal communication
Somatic gain-of-function HIF-2α (*HIF2A*) mutation

**HIF-2α target genes**

**NAM**: normal adrenal medulla
The story of the new syndrome continues: Ocular findings

NIH patients were found to have ocular abnormalities: Zhuang-Pacak syndrome…?

Left eye (2013)

- Hard exudate
- Fibrosis
- Macular edema
- Disc swelling

Right eye (2013)

- Retinal neovascularization
- Mild disc swelling

32 y. o. F presented to NIH with no visual symptoms

Zhuang-Pacak syndrome…?