SDHB-related Paragangliomas

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Riyadh, Saudi Arabia
No thing to disclose
Agenda

• Introduction
• Historical background
• SDHB-related PPGL
• Review some of our work
• Present some challenging SDHB-related PPGL
Definitions

Pheochromocytoma: intraadrenal NE tumors
Paragangliomas: extraadrenal Pheo

PGL and Pheo are different in many aspects and their distinction is important
Locations

Head/neck:
  • Carotid body (chemodectomas)
  • glomus jugulare

Mediastinal PGL

Abdominal PGL

Adrenal medulla: pheochromocytoma

Other sites: Lungs, liver, bladder, others
History

In 1886, Felix Fränkel wrote the first description of a patient with pheochromocytoma.
The Patient and Her Disease (translated and summarized from the Fränkel report)

The patient was born in 1865 and lived in Wittenweier near Lahr in the Black Forest region, 40 km north of Freiburg. Her parents and six brothers were healthy. Her illness began in the winter of 1883, when she was 18 years of age. It was characterized by three attacks of sudden-onset palpitations, anxiety, dizziness, headache, vomiting, constipation, and increasing weakness. She was hospitalized on December 11, 1884, and died 10 days later. When she presented, she was noted to be fairly malnourished, pale, with “agitated heart action and strong pulse,” epigastric pulsations, photophobia, and mydriatic pupils. Urinalysis revealed proteinuria, casts, and microhematuria. Retinoscopy revealed papilledema, yellow-white infiltrations, whitish stippling, multiple hemorrhages, and edema of the macula. During her inpatient stay, she had paroxysmal tachycardia (up to 180 beats per minute), sweating attacks, headaches, vomiting, visual deterioration, arrhythmia, nosebleeds, anxiety, and, in the end, severe chest pains.
Max Schottelius was the first to describe the pathological appearance of pheochromocytoma (Frankael’s patient).

“The brown appearance after exposure to chromate-containing Mueller’s fixative. This color change, known as chromaffin reaction, results from oxidation of catecholamines.”

The term "pheochromocytoma" was first coined by Ludwig Pick, a German pathologist, in 1912.

Greek: *phaios* (dark), *chroma* (color), *kytos* (cell), and *-oma* (tumor).
History

In 1926, César Roux (in Switzerland) and Charles Horace Mayo (in the U.S.A.) were the first surgeons to successfully remove pheochromocytomas.
Evidence of MEN-2 in the Original Description of Classic Pheochromocytoma

Hartmut P.H. Neumann, M.D., Alexander Vortmeyer, M.D., Dieter Schmidt, M.D., Martin Werner, M.D., Zoran Erlic, M.D., Alberto Cascon, Ph.D., Birke Bausch, M.D., Andrzej Januszewicz, M.D., and Charis Eng, M.D., Ph.D.

N Engl J Med
Volume 357(13):1311-1315
September 27, 2007
Germ-Line RET Cys634Trp Mutation in the Grandnephew of the Proband

Pheo: ‘Rule of 10’

10% extra-adrenal
10% occur in children
10% bilateral or multiple (more if familial)
10% recur (more if extra-adrenal)
10% malignant
10% hereditary

40-50% are hereditary
Familial Pheo/Para

- Neurofibromatosis type 1 (NF1)
- MEN 2a and MEN 2b (RET)
- Von Hippel-Lindau (VHL) syndrome
Hereditary PGL of the head and neck are associated with germ line mutation of mitochondrial complex II gene, succinyl dehydrogenase sub unit D (SDHD)
Mutations in SDHC cause autosomal dominant paraganglioma, type 3

Neurofibromin paragangliomas (FGA) are usually benign, neurocristod derived, slow-growing tumors of parasympathetic ganglia. Between 10% and 50% of cases are familial and are transmitted as autosomal dominant traits with incomplete penetrance.

In most hereditary cases, the trait is transmitted through affected fathers, but not through affected mothers, suggesting maternal imprinting (inactivation) of the disease gene. Hereditary paragangliomas is genetically heterogeneous and three loci, PGL1 (refs 3-5), PGL2 (ref. 6) and PGL3 (ref. 6), have been reported.

Mutations of SDHC, encoding the small subunit of cytochrome b in mitochondrial complex II (ref. 7), underlie PGL1. This complex contains four nuclear-encoded proteins. Subunits SDHA and SDHB constitute the catalytic domain and are anchored in the inner mitochondrial membrane by subunits SDHC and SDHD.

We reasoned that mutations in different components of mitochondrial complex II might cause other types of paraganglioma, and set out to sequence SDHC, SDHD, and SDHB in patients from a family with the non-maternally imprinted paraganglioma type 3 (PGL3, ref. 6).

Members of the family with PGL3 are shown (Fig. 1a). We analysed SDHC in both affected and unaffected family members at both the cDNA and the genomic level. We first synthesized cDNA by RT-PCR from lymphoblastoid cell lines of patients. Sequencing the entire cDNA of 310 bp (accession number D85772) did not reveal a mutation. Because a potentially mutated transcript might not be

Gene Mutations in the Succinate Dehydrogenase Subunit SDHB Cause Susceptibility to Familial Pheochromocytoma and to Familial Paraganglioma

Dewi Astuti,1 Farida Latif,1 Ashraf Dallol,2 Patricia L. M. Dahia,3 Fiona Douglas,1 Emad George,4 Filip Sköldberg,5 Eysteinn S. Husebye,5 Charis Eng,6 and Eamonn R. Maher1

1Section of Medical and Molecular Genetics, Department of Paediatrics and Child Health, University of Birmingham, Birmingham, England; 2Department of Cancer Biology, Dana-Farber Cancer Institute, Boston; 3Northern Regional Genetics Service, Royal Victoria Infirmary, Newcastle upon Tyne, England; 4Department of Medicine, King's College Hospital, London, England; 5Department of Medical Sciences, Uppsala University, Uppsala, Sweden; and 6Clinical Cancer Genetics and Human Cancer Genetics Program, Comprehensive Cancer Center, and the Division of Human Genetics, Department of Internal Medicine, The Ohio State University, Columbus; and CRC Human Cancer Genetics Research Group, University of Cambridge, Cambridge

SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma

Huai-Xiang Hao,1 Oleh Khalimonchuk,1,2 Margit Schraders,5,6 Noah Dephoure,7 Jean-Pierre Bayley,8 Henricus Kunst,7 Peter Devilee,8,9 Cor W. R. J. Cremers,7 Joshua D. Schiffmann,7 Brandon G. Bentz,4 Steven P. Gygi,7 Dennis R. Winge,1,2 Hanne Kremer,5,6 Jared Rutter1

Human Molecular Genetics, 2010, Vol. 19, No. 15
Advance Access published on May 18, 2010

SDHA is a tumor suppressor gene causing paraganglioma

Nelly Burnichon1,2,3,1, Jean-Jacques Brière4,5, Rosella Libé6,5,8, Laure Vescovo6, Julie Rivièrè2,3, Frédérique Tissier5,7,9, Eudice Jouanno1, Xavier Jeuneemaître1,2,3, Paule Benit1,10,11, Alexandre Tzagoloff1, Pierre Rustin10,11, Jérôme Berthelot2,5,8, Judith Favé3,3 and Anne-Paule Gimenez-Roquepo1,2,7

Chromatin remodeling genes

CSDE1, UBF, MAML3, GTF2I, IRP1

HIF2A, HIF2B, PHD1, PHD2, PHD3, PHD4, HIF1A
SDHB mutations (first discovery)

Genetic testing in Pheo/Paraganglioma

RET  
NF1  
VHL  
SDHD  
SDHB  
SDHC  
SDHA  
SDHAF2  
MAX  
TMEM127  
EPAS1  
FH

Fishbein, L and Nathanson K, Cancer genetics, 205:1-11;2012
TCGA data

25 Genes

<table>
<thead>
<tr>
<th>Genes</th>
<th>Alteration %</th>
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<tr>
<td>SDHB</td>
<td>9%</td>
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<tr>
<td>VHL</td>
<td>4%</td>
</tr>
<tr>
<td>RET</td>
<td>6%</td>
</tr>
<tr>
<td>NF1</td>
<td>3%</td>
</tr>
<tr>
<td>SDHD</td>
<td>2%</td>
</tr>
<tr>
<td>MAX</td>
<td>1%</td>
</tr>
<tr>
<td>TMEM127</td>
<td>0.6%</td>
</tr>
<tr>
<td>EGLN1</td>
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</tr>
<tr>
<td>HRAS*</td>
<td>10%</td>
</tr>
<tr>
<td>NF1*</td>
<td>9%</td>
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<tr>
<td>EPAS1*</td>
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<tr>
<td>RET*</td>
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<td>CSDE1*</td>
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<td>SETD2</td>
<td>2%</td>
</tr>
<tr>
<td>VHL</td>
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</tr>
<tr>
<td>FGFR1</td>
<td>1%</td>
</tr>
<tr>
<td>TP53</td>
<td>0.6%</td>
</tr>
<tr>
<td>BRAF</td>
<td>0.6%</td>
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<tr>
<td>ATRX</td>
<td>3%</td>
</tr>
<tr>
<td>ARNT</td>
<td>1%</td>
</tr>
<tr>
<td>IDH1</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fusion Genes</th>
<th>Alteration %</th>
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</thead>
<tbody>
<tr>
<td>MAML3</td>
<td>5%</td>
</tr>
<tr>
<td>BRAF</td>
<td>0.6%</td>
</tr>
<tr>
<td>NGFR</td>
<td>0.6%</td>
</tr>
<tr>
<td>NF1</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Genetics


- NF1
- VHL
- SDHD
- SDHC
- SDHB
- TMEM127
- SDHAF2
- PHD2
- SDHA
- MAX
- H-RAS
- PHD1
- MDH2
- ATRX
- IRP1
- CSDE1
- UBF1-MAML3
- GOT2
Table 1. Penetration of cluster 1–related PPGLs

<table>
<thead>
<tr>
<th>Penetration</th>
<th>SDHB</th>
<th>SDHA</th>
<th>SDHC</th>
<th>SDHD</th>
<th>VHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 years</td>
<td>21%</td>
<td></td>
<td>43%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 years</td>
<td>42% and 22%, respectively</td>
<td>1.7%</td>
<td></td>
<td>15-20%</td>
<td></td>
</tr>
<tr>
<td>80 years</td>
<td>25-65%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lifetime estimate</td>
<td>22%</td>
<td>8.3%</td>
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</table>

Table 2. Metastatic risk and location of cluster 1–related PPGLs

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Metastatic risk</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDHB</td>
<td>35-75%</td>
<td>Sympathetic/parasympathetic PGLs, less commonly PCCs</td>
</tr>
<tr>
<td>SDHA</td>
<td>30-66%</td>
<td>Sympathetic/parasympathetic PGLs, very rarely PCCs</td>
</tr>
<tr>
<td>SDHC</td>
<td>low</td>
<td>Sympathetic/parasympathetic PGLs, less commonly PCCs</td>
</tr>
<tr>
<td>SDHD</td>
<td>15-29%</td>
<td>Sympathetic/parasympathetic (often head and neck) PGLs and PCCs</td>
</tr>
<tr>
<td>HIF2A/EPAS1</td>
<td>&gt;30%</td>
<td>Sympathetic/rarely parasympathetic PGLs and PCCs</td>
</tr>
<tr>
<td>VHL</td>
<td>5-8%</td>
<td>PCCs, less commonly sympathetic PGLs, and rarely parasympathetic PGLs</td>
</tr>
<tr>
<td>SDHAF2</td>
<td>not known</td>
<td>Parasympathetic (head and neck) PGLs</td>
</tr>
</tbody>
</table>

Interestingly, although 70% of children with SDHB-related tumors developed metastases at a median age of 16, the estimated 5-, 10-, and 20-year overall survival rate was relatively favorable (100%, 97%, and 78%, respectively) (61). Recent studies consistently report that apart from the absence of metastases, both younger age (<40 years in one study) and smaller size of the primary tumor (<5 cm) at first diagnosis is associated with a better prognosis and survival (1, 3, 23, 37).

Of note, among the cluster 1 group there are some notable differences in prevalence for certain tumor locations.
# Follow up of asymptomatic SDHx carriers

## Adults
- Clinical examination (BP)
- Biochemical testing
- MRI (Head-pelvis)
- \(^{68}\text{Ga PET CT}\)

### Every 12 months
- Clinical examination (BP)
- Biochemical testing

### Every 24-36 months
- MRI (Head-pelvis)
- \(^{68}\text{Ga PET CT}\)

## Children
- Clinical examination (BP)
- Biochemical testing
- MRI (Head-pelvis)
- \(^{68}\text{Ga PET CT}\)

**SDHB: 6-10 years, Other SDHx: 10-15 years**

### Every 12 months
- Clinical examination (BP)
- Every 24 months
  - Biochemical testing

### Every 24-36 months
- MRI (Head-pelvis)

---

Management of SDHx mutation carriers (Children)

Children (<18 years old) with mutations in SDHA, SDHB, SDHC or SDHD-pi

Initial screening
- Blood pressure measurements, symptoms questionnaire
- Measure levels of plasma free metanephrines or urinary metanephrines
- Head and neck MRI
- Thoracic, abdominal and pelvic MRI

Negative initial screening

Every year
- Blood pressure measurements, symptoms questionnaire

Every 2 years
- Measure levels of plasma free metanephrines or urinary metanephrines

Every 2–3 years
- Head and neck MRI and thoracic, abdominal and pelvic MRI

Management of SDHx mutation carriers (adults)

Mutational profile and genotype/phenotype correlation of non-familial pheochromocytoma and paraganglioma

Shatha Albattal1,6, Meshael Alswailem1, Yosra Moria2, Hindi Al-Hindi3, Majed Dasouki4,5, Mohamed Abouelhoda4,5, Hala Aba Alkhail3, Entissar Alsuhaibani6 and Ali S. Alzahrani1,2

1Department of Molecular Oncology, King Faisal Specialist Hospital and Research Centre, Riyadh 11211, Saudi Arabia
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3Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh 11211, Saudi Arabia
4Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh 11211, Saudi Arabia
5Saudi Human Genome Program, King Abdulaziz City for Science and Technology, Riyadh 11211, Saudi Arabia
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Keywords: pheochromocytoma; paraganglioma; mutations; NGS; SDHB

Received: June 24, 2019   Accepted: August 16, 2019   Published: October 15, 2019
Clinical and pathological features

Table 1: Age, sex and pathological features of 101 cases of PPGL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number or Frequency</th>
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<tbody>
<tr>
<td>Age (yrs) median (Range)</td>
<td>38 (8–81)</td>
</tr>
<tr>
<td>Sex F: M</td>
<td>61:40</td>
</tr>
<tr>
<td>Tumor size (cm), Median (Range)</td>
<td>5 (1–24)</td>
</tr>
<tr>
<td>Vascular Invasion</td>
<td>10 (9.9%)</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>19 (18.8%)</td>
</tr>
<tr>
<td>Distant Metastasis</td>
<td>10 (9.9%)</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
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<tr>
<td>PCC (4 Bilateral)</td>
<td>32 (31.7%)</td>
</tr>
<tr>
<td>Abdominal PGL</td>
<td>26 (25.7%)</td>
</tr>
<tr>
<td>Head/Neck PGL (2 bilateral)</td>
<td>39 (38.6%)</td>
</tr>
<tr>
<td>Other sites</td>
<td>2 (1.99%)</td>
</tr>
<tr>
<td>Multiple sites (including 4 bilateral PCC and 2 bilateral head/neck PGL)</td>
<td>8 (7.9%)</td>
</tr>
</tbody>
</table>

Albattal, S et al. Oncotarget, 2019, 10;5919-5931
Figure 1: Pie diagram showing the distribution and number of cases with germline mutations in different gene.

Albattal S, et al. Oncotarget, 2019, 10;5919-5931
One genotype, many phenotypes: *SDHB* p.R90X mutation-associated paragangliomas

Ali S. Alzahrani¹,² • Meshael Alswailem² • Yosra Moria¹ • Ayman Aldeheshi³ • Hindi Al-Hindi³

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### Features of 13 cases with SDHB R90* mutation

<table>
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<tr>
<th>No.</th>
<th>Age at Dx</th>
<th>Sex</th>
<th>Family Hx</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Distant Mets.</th>
<th>Initial Tx</th>
<th>Additional Tx</th>
<th>Outcome</th>
<th>Duration (years)</th>
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<td>1</td>
<td>23</td>
<td>F</td>
<td>Yes</td>
<td>Abdomen</td>
<td>5</td>
<td>Yes</td>
<td>Sx</td>
<td>Sx, MIBG, VCD</td>
<td>Death</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>M</td>
<td>Yes</td>
<td>Abdomen</td>
<td>10</td>
<td>Yes</td>
<td>VCD</td>
<td>Pazopanib</td>
<td>Progression</td>
<td>1.8</td>
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<td>24</td>
<td>M</td>
<td>Yes</td>
<td>Abdomen</td>
<td>12</td>
<td>Yes</td>
<td>VCD</td>
<td>Lu\textsuperscript{177}, Sorafenib</td>
<td>Death</td>
<td>4</td>
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<tr>
<td>4</td>
<td>24</td>
<td>M</td>
<td>Yes</td>
<td>Abdomen</td>
<td>13</td>
<td>Yes</td>
<td>Sx</td>
<td>MIBG, XRT</td>
<td>Progression</td>
<td>14</td>
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<tr>
<td>5</td>
<td>36</td>
<td>M</td>
<td>No</td>
<td>Abdomen and head</td>
<td>18</td>
<td>Yes</td>
<td>Sx</td>
<td>MIBG, XRT</td>
<td>Death</td>
<td>6</td>
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<tr>
<td>6</td>
<td>21</td>
<td>M</td>
<td>No</td>
<td>Abdomen</td>
<td>10</td>
<td>Yes</td>
<td>Sx</td>
<td></td>
<td>Death</td>
<td>4</td>
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<td>7</td>
<td>23</td>
<td>F</td>
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<td>Abdomen</td>
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<td>No</td>
<td>Sx</td>
<td></td>
<td>Recurrence</td>
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<td>8</td>
<td>10</td>
<td>F</td>
<td>No</td>
<td>Abdomen</td>
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<td>No</td>
<td>Sx</td>
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<td>Remission</td>
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<td>Adrenal</td>
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<td>No</td>
<td>Sx</td>
<td></td>
<td>Remission</td>
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<td>10</td>
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<td>No</td>
<td>Neck (carotid)</td>
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<td></td>
<td>Remission</td>
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<td>11</td>
<td>8</td>
<td>F</td>
<td>No</td>
<td>Abdomen</td>
<td>3</td>
<td>No</td>
<td>Sx</td>
<td></td>
<td>Remission</td>
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<td>12</td>
<td>17</td>
<td>M</td>
<td>No</td>
<td>Abdomen</td>
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<td>No</td>
<td>Sx</td>
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<td>Remission</td>
<td>6</td>
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<td>13</td>
<td>M</td>
<td>No</td>
<td>Abdomen</td>
<td>13</td>
<td>No</td>
<td>Sx</td>
<td></td>
<td>Remission</td>
<td>9</td>
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</table>


One genotype, multiple phenotypes

Face 1: Same SDHB mutation, different response to the same chemotherapy
Case 1

- A 37-year old man
- Referred as a case of nasopharyngeal cancer

Face 2: unusual location of SDHB-related PGL masquerading as NP cancer or pituitary adenoma
MULTIPLE PARAGANGLIOMA SYNDROME TYPE 4 DUE TO Succinate Dehydrogenase B Mutation: Diagnostic and Therapeutic Challenges of a Skull Base Paraganglioma Masquerading as Nasopharyngeal Cancer

Ali S. Alzahrani, MD, FACE; Omalkhaire Alshailkh, MD; Muhammad Faizy-Ul-Haque, PhD; Halah Abalkhail, PhD; Fouad Al-Dayer, MD; Hadi Al Hindi, MD

SDHB-Normal

SDHB-R90X Mutation

Alzahrani A, et al, Endocrine Practice 16(3):452-8
Case 2: A novel mutation and a novel manifestation

Familial paraganglioma due to a novel SDHB mutation: familial phenotypic heterogeneity and a potentially novel manifestation

Ali S Alzahrani*1,2, Meshael Alswailim2, Shatha Albatal2, Ebtesam Qasem2, Avanyapuram K Murugan2 & Hindi Al-Hindi3

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2Department of Molecular Oncology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia
3Department of Pathology & Laboratory Medicine, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia

*Author for correspondence: aliz@kfshrc.edu.sa
A novel *SDHB* mutation (c.409A>G, p.K137E)
July 2023

FNA: Papillary thyroid cancer

Total thyroidectomy: 1.4 cm PTC with 4 vessel angioinvasion

Is thyroid cancer related to SDHB?
Case 3

A 56-year old man

Multiple para/pheo
  • Pheo at age 20 yrs
  • Mediastinal PGL at age 32 yrs
  • Carotid body tumor at age 36 yrs

Face 4: Living most of his life with persistent and recurrent PGL + polycythemia
MIBG scan
**SDHB**: c.689G>A, p.Arg230His

<table>
<thead>
<tr>
<th>Gene / Variant</th>
<th>Genotype</th>
<th>ACMG Classification</th>
<th>Mode of Inheritance</th>
<th>Phenotype</th>
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</thead>
<tbody>
<tr>
<td><strong>SDHB</strong></td>
<td>Heterozygous</td>
<td>Pathogenic</td>
<td>Dominant</td>
<td>Paragangliomas 4, OMIM# 115310 (3), Autosomal dominant; Pheochromocytoma, OMIM# 171300 (3), Autosomal dominant; Paraganglioma and gastric stromal sarcoma, OMIM# 606864 (3)</td>
</tr>
</tbody>
</table>
Is polycythemia related to SDHB variant, PGL or coincidental?
An aggressive cabergoline-resistant, temozolomide-responsive macroadenoma due to a germline $SDHB$ pathogenic variant in the absence of paraganglioma or pheochromocytoma

Ali S. Alzahrani$^{1,2*}$, Abdulghani Bin Nafisah$^{1,3}$, Meshael Alswailem$^1$, Yosra Moria$^2$, Dagmara Poprawski$^{4,5}$, Hindi Al-Hindi$^6$ and Karel Pacak$^{7,8}$
Sequential coronal (upper panels) and sagittal (lower panels) enhanced T1 weighted MR Images of macroprolactinoma at several stages (arrows) as follows: (A) before first trans sphenoidal surgery (TSS), (B) before second TSS, (C) immediately after Second surgery, (D) 4 months after second TSS presenting with bleeding in PA, and (E) 4 months after XRT.
FIGURE 3
Sequential coronal and sagittal enhanced T1-weighted MR images showing the changes in the size of the macroadenoma (arrows) after starting temozolomide (TMZ): (A) at baseline just before starting TMZ, (B) 4 months later, (C) after 11 months on TMZ and (D) 7 months after discontinuation of TMZ.
FIGURE 4
Prolactin levels over time showing the non-response to cabergoline and trans sphenoidal surgery and the dramatic response to TMZ.
FIGURE 5
Chromatograms of part of SDHB exon 4 showing wild type sequence (upper panel), leucocyte DNA sequence (middle panel) showing a heterozygous germline mutation (NM_003000, c.343C>T) and pituitary adenoma (somatic) DNA sequence (lower panel) showing the same mutation in a homozygous form (loss of heterozygosity).
Case 5

- AA was a 28-year old man without family history of PPGL
- Had varicocele in 2017 (surgically treated)
- Recurrent varicocele 2019
- CT scan of the abdomen: a large mass 12x8x6.5 cm
- No symptoms at all.
- Urine metanephrines: normal x 3
• Biopsy of thyroid nodule: pap. Thyroid cancer
• Underwent surgical resection of PGL IN February 2020
• 11 cm PGL locally invasive with vascular invasion, Ki67 40%
• August 2020: total thyroidectomy
• Pathology: tall cell variant PTC, bilateral, multifocal, largest 1.5 cm
• 11/16 Lymph nodes positive for mets
• Received I131 therapy for PTC
• Received 6 doses of Lu177 between March-October 2022
• External radiotherapy 5 sessions left 9th rib area
• Stable for the last 14 months
(A) Germline

SDHB: R230C (het)

(B) Papillary Thyroid Cancer

BRAF: V600E

SDHB: R230C (het)

C250C

TERT: -ve

C228C

(C) Paraganglioma

BRAF: -ve

SDHB: R230C (hom)

TERT: C228T
Non-PPGL tumors in SDHB mutations

- GIST tumors
  - 85-90%: KIT, PDGFRA
  - 5-7.5%: NF1, BRAF
  - 5-7.5%: SDHB-negative IHC (mostly gastric, multifocal, may involve LN, indolent course)
    - Sporadic
    - Carney Stratakis syndrome: PGL, GIST
    - Carney’s triad: PGL, GIST and pulmonary chondroma

- RCC (0.05-0.2% of all RCC are SDHx-related)
  - Young age < 40 years, multiple, bilateral, recurrent
  - Cytoplasmic vacuoles and inclusion-like spaces, oncocytic
Non-PPGL tumors in SDHB mutations

- Pituitary adenoma
  - Rare
  - About 21 cases reported in the literature
  - Only 5 cases had further studies to confirm pathogenesis of SDHB

- Other tumors:
  - Papillary thyroid cancer: questionable
  - Lymphoid malignancy: two cases (SDHB, SDHC but with positive SDHB staining)
  - Pancreatic NET: in asymptomatic SDHD carrier
Thank you
Follow up of patients with Hx of SDHx-related PPGL

Table 5. Follow-up of cluster 1A/1B mutation carriers with a history of a PPGL

<table>
<thead>
<tr>
<th>Follow-up of cluster 1 mutation carriers with a history of a PPGL</th>
<th>History of metastatic PPGL, history of sympathetic PGL, SDHA/B, FH HIF2A/EPAS1-related PPGLs</th>
<th>History of head and neck PGL, SDHC/D/AF2, VHL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemistry</strong></td>
<td>6-12 months (for HIF2A/EPAS1 including hematocrit)</td>
<td>12 months</td>
</tr>
<tr>
<td>Imaging (MRI base of the skull to pelvis, possibly alternating with low-dose chest CT plus MRI base of the skull, neck, abdomen, pelvis)</td>
<td>12-24 months (initially 12, then 12-24 months)</td>
<td>24-36 months (24 months for SDHD) VHL mutations: risk of renal cell cancer, consider abdominal MRI every 12 months; optic fundus examination every 12 months; CNS tumors, CNS MRI every 24-36 months.</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; PGL, paraganglioma; PPGL, pheochromocytoma/paraganglioma.

<table>
<thead>
<tr>
<th>Ongoing studies</th>
<th>Therapy</th>
<th>Patient number (n)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04394858</td>
<td>PARP inhibitor olaparib plus temozolomide (phase II, prospective)</td>
<td></td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01850888</td>
<td>[131I]-MIBG</td>
<td></td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT00107289</td>
<td>[131I]-MIBG (phase II, prospective)</td>
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<td>Recruiting</td>
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<tr>
<td>NCT04029428</td>
<td>[177Lu]-DOTATATE vs [131I]-DOTATATE vs mix each of 50% (PRRT) (phase II, prospective)</td>
<td></td>
<td>Recruiting (SDHx-related and sporadic PPGLs)</td>
</tr>
<tr>
<td>NCT03206069</td>
<td>[177Lu]-DOTATATE (Lutathera) (PRRT) (phase II, prospective)</td>
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<td>Recruiting</td>
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<tr>
<td>NCT04276597</td>
<td>[177Lu]-DOTATOC (PRRT) (phase II, prospective)</td>
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<td>Recruiting</td>
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<tr>
<td>NCT04711135</td>
<td>[177Lu]-DOTATATE (Lutathera) (PRRT) in adolescents (phase II, prospective)</td>
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<td>Not yet recruiting</td>
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<td>NCT03923257</td>
<td>[177Lu]-DOTATATE (PRRT) in children and adolescents (phase I/III, prospective)</td>
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<td>Recruiting</td>
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<tr>
<td>LAMPARA</td>
<td>Lantreotide (cold somatostatin analog)</td>
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<td>Not yet recruiting</td>
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<td>NCT03946527</td>
<td>(phase II, prospective)</td>
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<td>Recruiting</td>
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<tr>
<td>NCT03034200</td>
<td>Dopamine receptor D2 and cascinolyl protease F (ClpP) agonist ONC201 (phase II, prospective)</td>
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<td>Recruiting</td>
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<tr>
<td>NCT04284774</td>
<td>Farnesyltransferase inhibitor tipifarnib (RAS inactivation) (phase II, prospective)</td>
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<td>Recruiting</td>
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<tr>
<td>FIRST-MAPP Study</td>
<td>TKI sunitinib (phase II, prospective, first randomized placebo-controlled study)</td>
<td>N = 74 (closed)</td>
<td>Data arriving soon</td>
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<tr>
<td>NCT01371201</td>
<td>TKI Axitinib (AG-013736) (phase II, prospective)</td>
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<td>Recruiting</td>
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<tr>
<td>NCT03008369</td>
<td>TKI lenvatinib (phase II, prospective)</td>
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<td>Active, not recruiting</td>
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<tr>
<td>NCT02120833</td>
<td>TKI cabozantinib (phase II, prospective)</td>
<td>N = 10</td>
<td>Recruiting (preliminary data from n = 10, partial response 40%, PFS 11.2)</td>
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<tr>
<td>NCT04400474</td>
<td>Cabozantinib plus atezolizumab (CABATEN) (phase II, prospective)</td>
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<td>Recruiting</td>
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<td>NCT02834013</td>
<td>Nivolumab plus ipilimumab (phase II, prospective)</td>
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<td>NCT02727132</td>
<td>Pembrolizumab (phase II, prospective)</td>
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<td>NCT04187404</td>
<td>Novel Therapeutic Vaccine (EO2401) (phase I/II, prospective)</td>
<td></td>
<td>Recruiting</td>
</tr>
</tbody>
</table>
Conclusions (Genetics)

Pheo/Para are unique oncometabolic genetic tumors

Major advances in genetics, biochemistry, imaging and therapy of Pheo/PGL

Genetic causes occur in about 70% of cases

Major advances in translational research in Pheo/PGL

A prototype for a real precision medicine practice