SDHB-related Paragangliomas

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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:

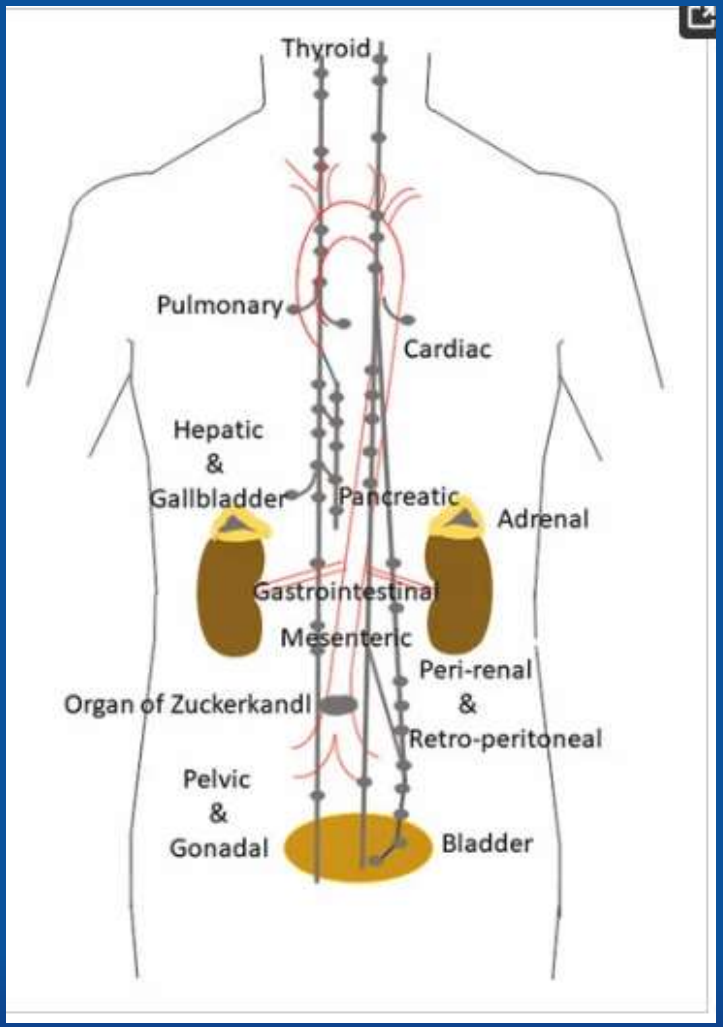
- Carotid body (chemodectomas)
- glomus jagulare

Mediastinal PGL

Abdominal PGL

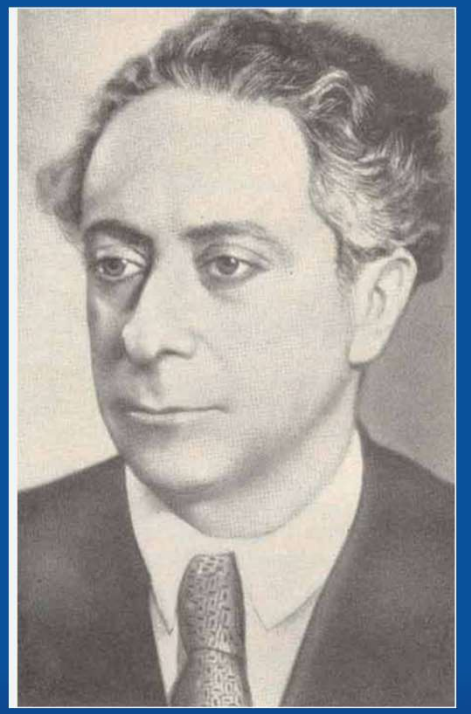
Adrenal medulla: pheochromocytoma

Other sites: Lungs, liver, bladder, others



History

In 1886, Felix Fränkel wrote the first description of a patient with pheochromocytoma



3. Fränkel F. Ein Fall von doppelseitigem, völlig latent verlaufenen Nebennierentumor und gleichzeitiger Nephritis mit Veränderungen am Circulationsapparat und Retinitis. Arch Pathol Anat Physiol Klin Med 1886;103:244-63.

Classics in Oncology

A Case of Bilateral, Completely Latent Adrenal Tumor and Concurrent Nephritis with Changes in the Circulatory System and Retinitis

Felix Fränkel, M.D.

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.

Neumann HPH et al. N Engl J Med 2007;357:1311-1315

Figure 2. Portrait of Max Schottelius.

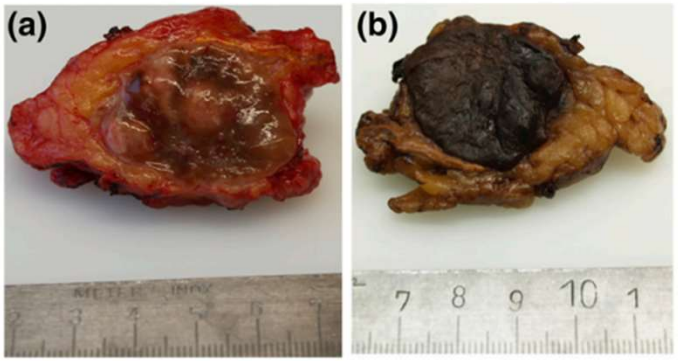


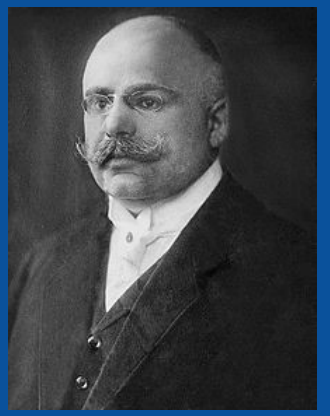
Figure 1. A selected pheochromocytoma fixed and stained by Mueller's solution. Shown is the macroscopic appearance of a cross-section through the middle of the tumor. (a) Unfixed and unstained. (b) Fixed and stained by Mueller's solution.

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

Max Schottelius was the first to describe the pathological appearance of pheochromocytoma (Frankael's patient)

Bausch B, et al, Journal of the Endocrine Society, 2017, 1(7);957–964

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

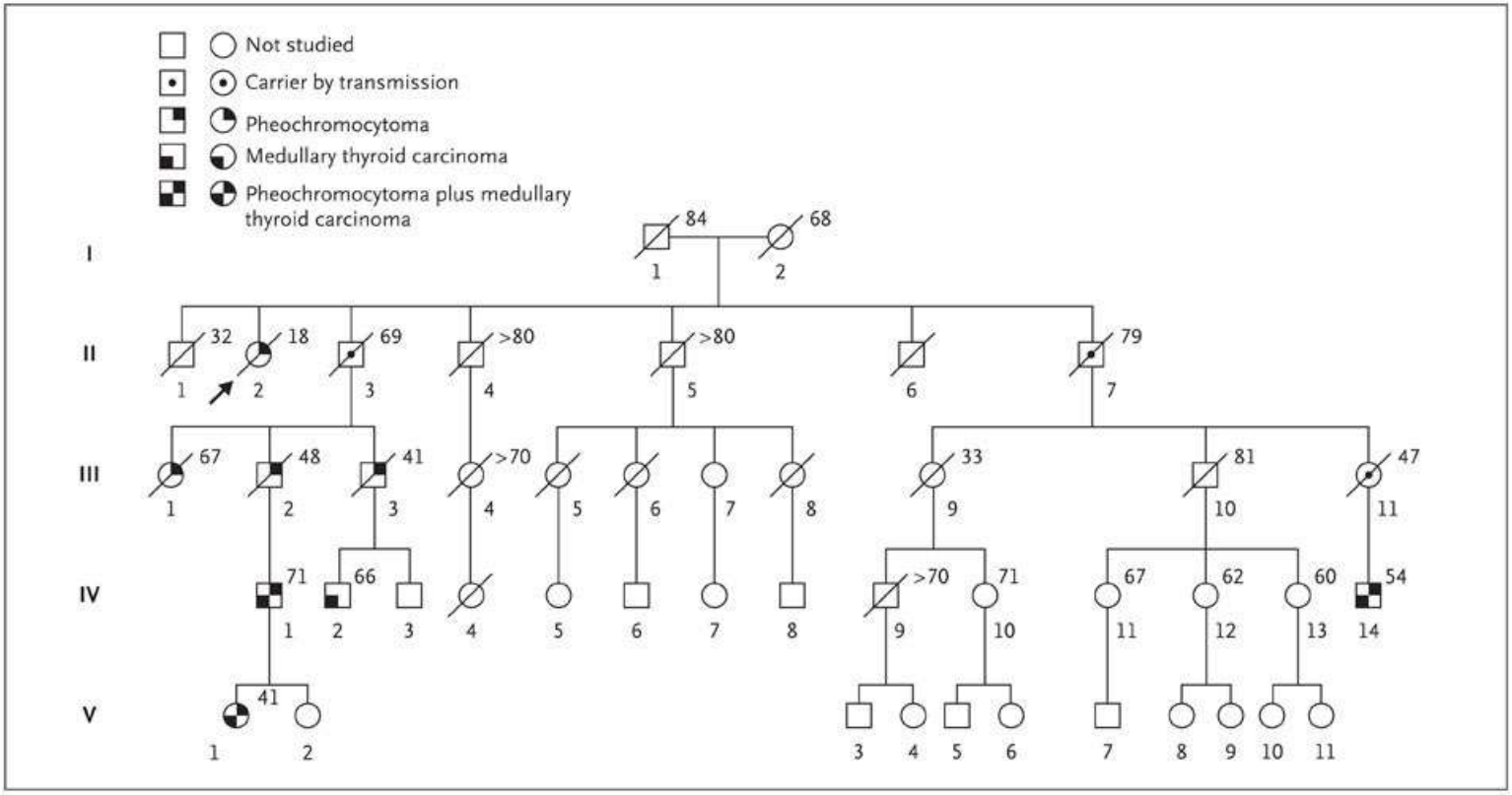
Original Article

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

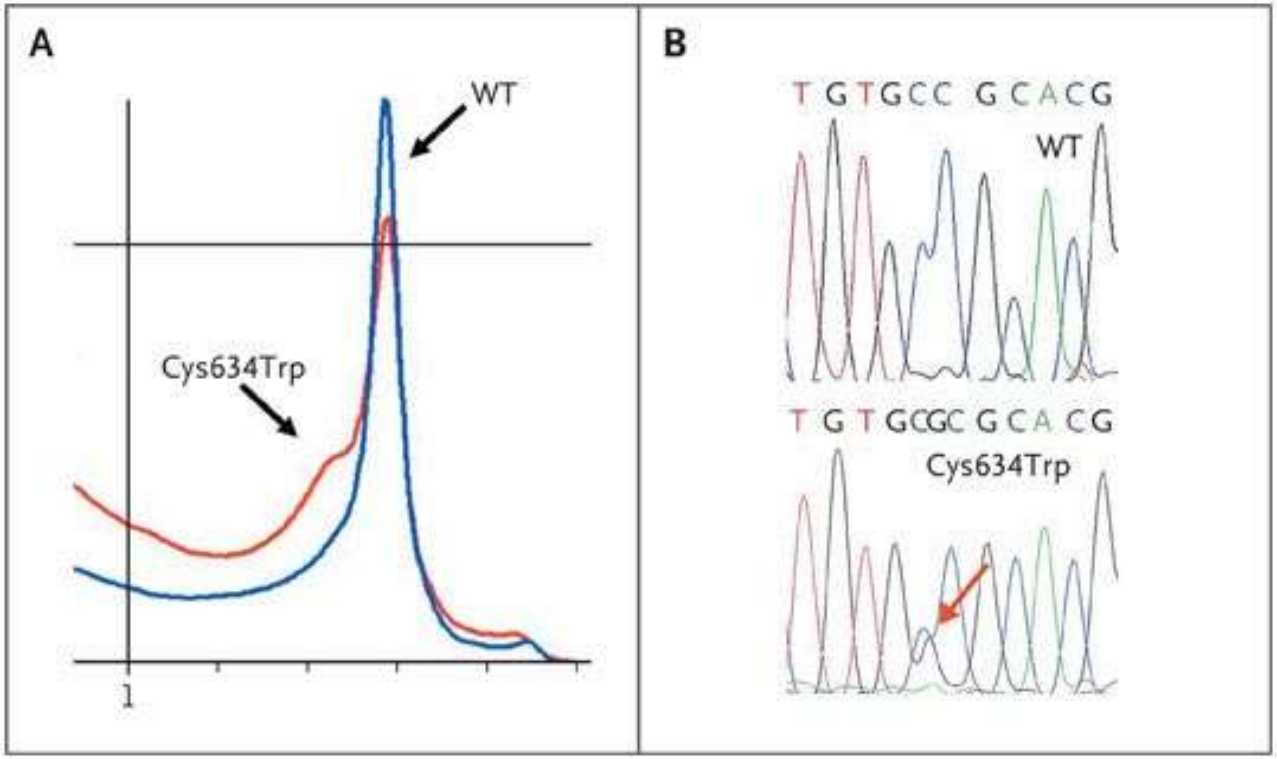
Pedigree of Proband's Extended Family



Neumann HPH et al. N Engl J Med 2007;357:1311-1315

The NEW ENGLAND JOURNAL of MEDICINE

Germ-Line RET Cys634Trp Mutation in the Grandnephew of the Proband



Neumann HPH et al. N Engl J Med 2007;357:1311-1315

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

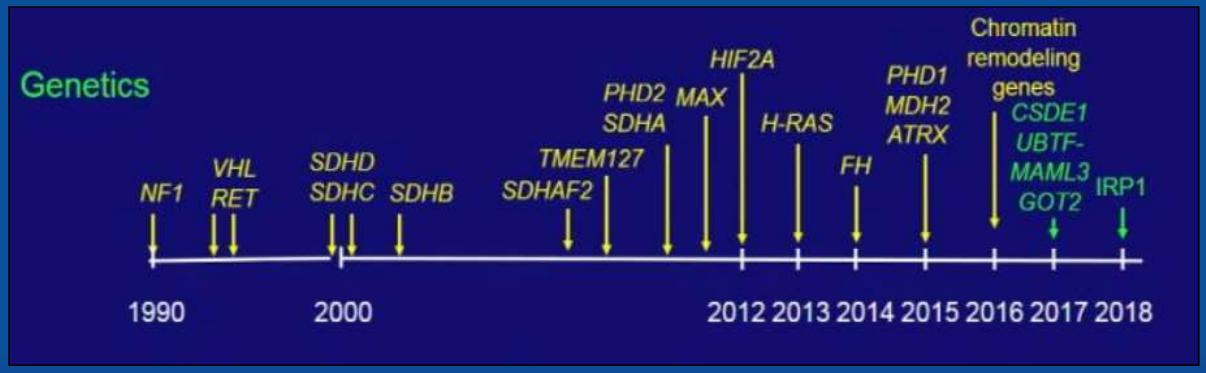
40-50% are hereditary

Familial Pheo/Para

Neurofibromatosis type 1 (NF1)

MEN 2a and MEN 2b (RET)

Von Hippel-Lindau (VHL) syndrome



REPORTS

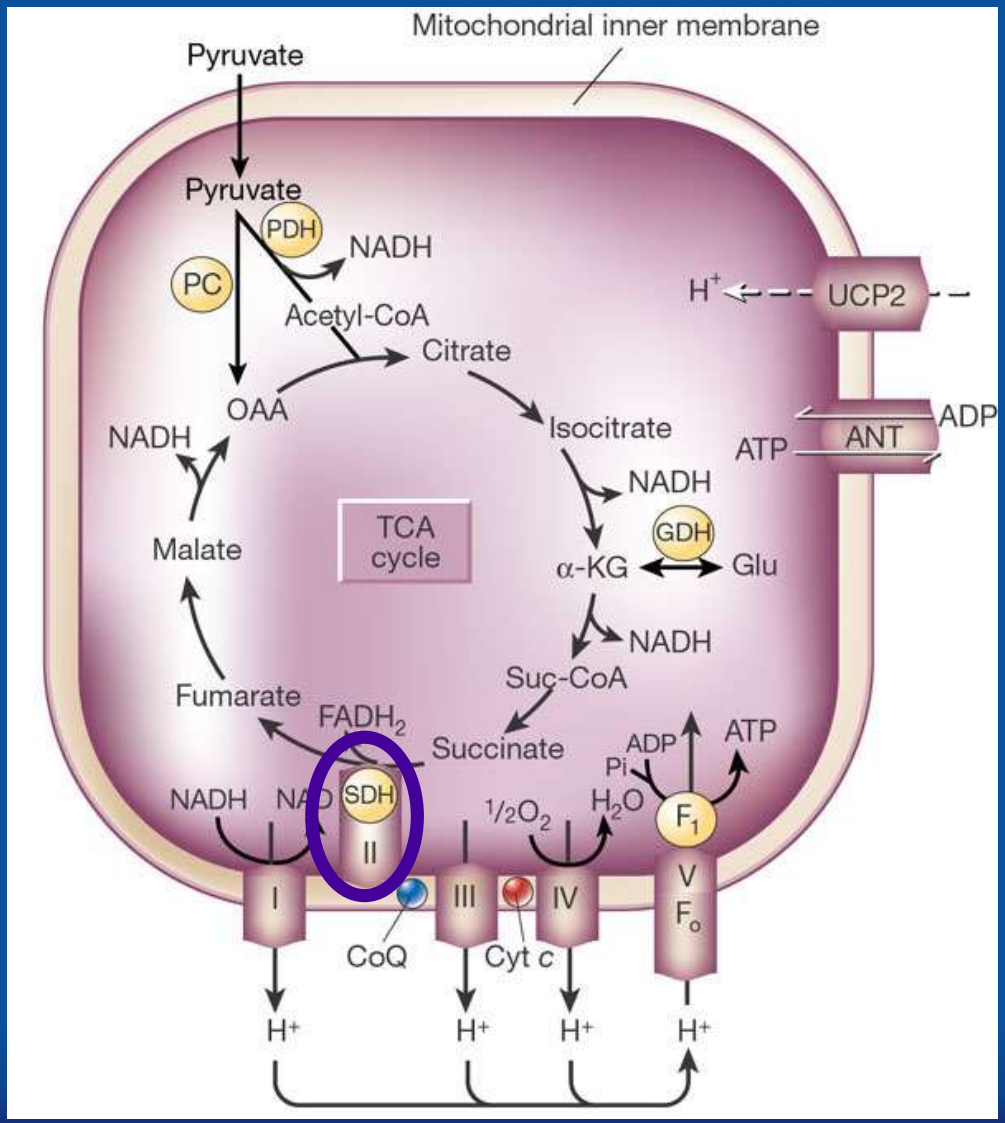
Mutations in *SDHD*, a Mitochondrial Complex II Gene, in Hereditary Paraganglioma

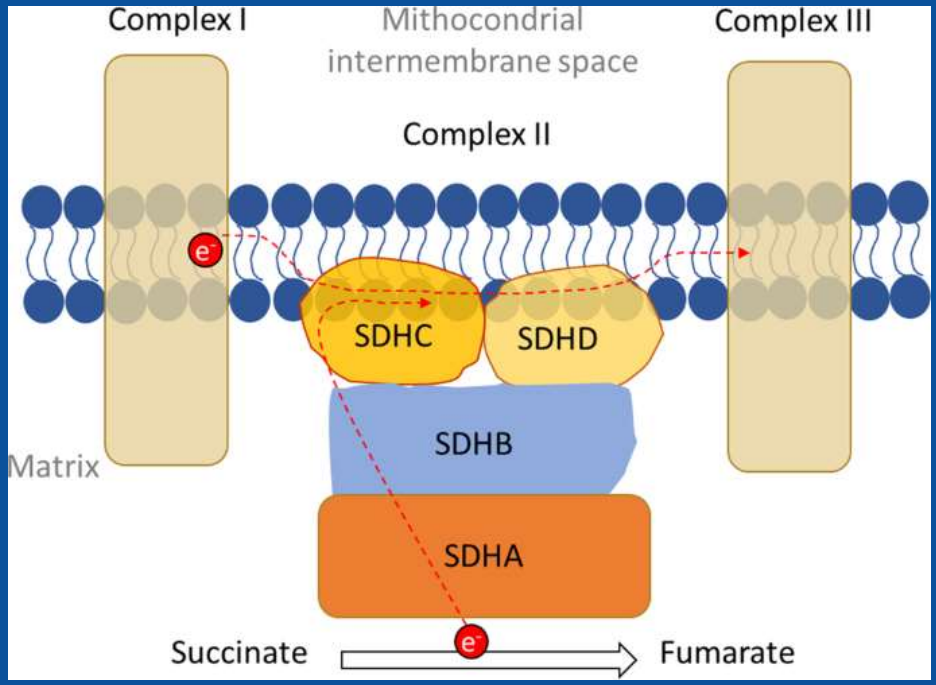
Bora E. Baysal,[1]* Robert E. Ferrell,[2] Joan E. Willett-Brozick,[1] Elizabeth C. Lawrence,[2] David Myssiorek,[5] Anne Bosch,[6] Andel van der Mey,[7] Peter E. M. Taschner,[6] Wendy S. Rubinstein,[3] Eugene N. Myers,[4] Charles W. Richard III,[9] Cees J. Cornelisse,[8] Peter Devilee,[6] B. Devlin[1]

Hereditary paraganglioma (PGL) is characterized by the development of benign, vascularized tumors in the head and neck. The most common tumor site is the carotid body (CB), a chemoreceptive organ that senses oxygen levels in the blood. Analysis of families carrying the *PGL1* gene, described here, revealed germ line mutations in the *SDHD* gene on chromosome 11q23. *SDHD* encodes a mitochondrial respiratory chain protein—the small subunit of cytochrome b in succinate-ubiquinone oxidoreductase (cybS). In contrast to expectations based on the inheritance pattern of PGL, the SDHD gene showed no evidence of imprinting. These findings indicate that mitochondria play an important role in the pathogenesis of certain tumors and that cybS plays a role in normal CB physiology.

Science, Feb 2000, Vol 287; 848-851

Hereditary PGL of the head and neck are associated with germ line mutation of mitochondrial complex II gene, succinyl dehydrogenase sub unit D(SDHD)


Mitochondrial inner membrane
Pyruvate
Pyruvate
PDH
NADH
PC
Acetyl-CoA
Citrate
OAA
Isocitrate
NADH
TCA cycle
GDH
α-KG
Glu
NADH
Suc-CoA
Malate
Fumarate
FADH2
Succinate
NADH
SDH
II
I
III
IV
CoQ
Cyt c
1/2O2
H2O
ADP
Pi
ATP
F1
V
Fo
H+
H+
H+
H+
H+
UCP2
ANT
ADP
ATP


Complex I
Mithocondrial intermembrane space
Complex III
Complex II
e-
SDHC
SDHD
SDHB
SDHA
Matrix
Succinate
Fumarate
e-

Mutations in *SDHC* cause autosomal dominant paraganglioma, type 3

Nonchromaffin paragangliomas (PGLs) are usually benign, neural-crest–derived, slow-growing tumours of parasympathetic ganglia. Between 10% and 50% of cases are familial and are transmitted as autosomal dominant traits with incomplete and age-dependent penetrance[1,2].

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 paraganglioma is genetically heterogeneous and three loci, *PGL1* (refs 3,4), *PGL2* (ref. 5) and *PGL3* (ref. 6), have been reported. Mutations of *SDHD*, 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 domains 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 analyse *SDHC*, *SDHA* 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. 1*a*). 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 510 bp (accession number D49737) did not reveal a mutation. Because a potentially mutated transcript might not be

Am. J. Hum. Genet. 69:49–54, 2001

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,[1] Patricia L. M. Dahia,[2] Fiona Douglas,[3] Emad George,[4] Filip Sköldberg,[5] Eystein S. Husebye,[5] Charis Eng,[6] and Eamonn R. Maher[1]

[1]Section of Medical and Molecular Genetics, Department of Paediatrics and Child Health, University of Birmingham, Birmingham, England; [2]Department of Cancer Biology, Dana-Farber Cancer Institute, Boston; [3]Northern Regional Genetics Service, Royal Victoria Infirmary, Newcastle upon Tyne, England; [4]Department of Medicine, Kings Lynn Hospital, Norfolk, England; [5]Department of Medical Sciences, Uppsala University, Uppsala, Sweden; and [6]Clinical Cancer Genetics and Human Cancer Genetics Programs, 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

Sciencexpress Report

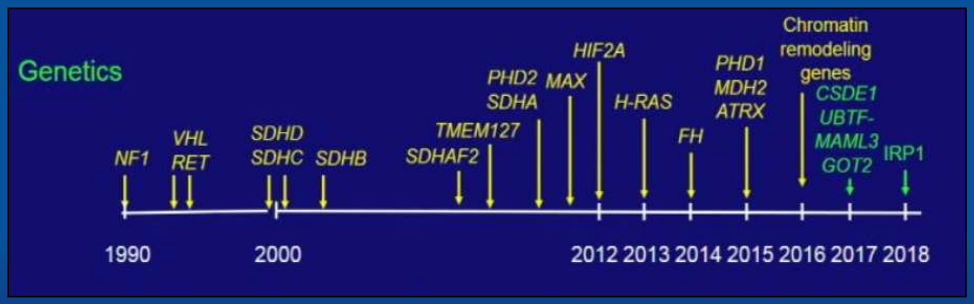
SDH5, a Gene Required for Flavination of Succinate Dehydrogenase, Is Mutated in Paraganglioma

Huai-Xiang Hao,[1] Oleh Khalimonchuk,[1,2] Margit Schraders,[5,6] Noah Dephoure,[7] Jean-Pierre Bayley,[8] Henricus Kunst,[5] Peter Devilee,[8,9] Cor W. R. J. Cremers,[5] Joshua D. Schiffman,[3] Brandon G. Bentz,[4] Steven P. Gygi,[7] Dennis R. Winge,[1,2] Hannie Kremer,[5,6] Jared Rutter[1*]

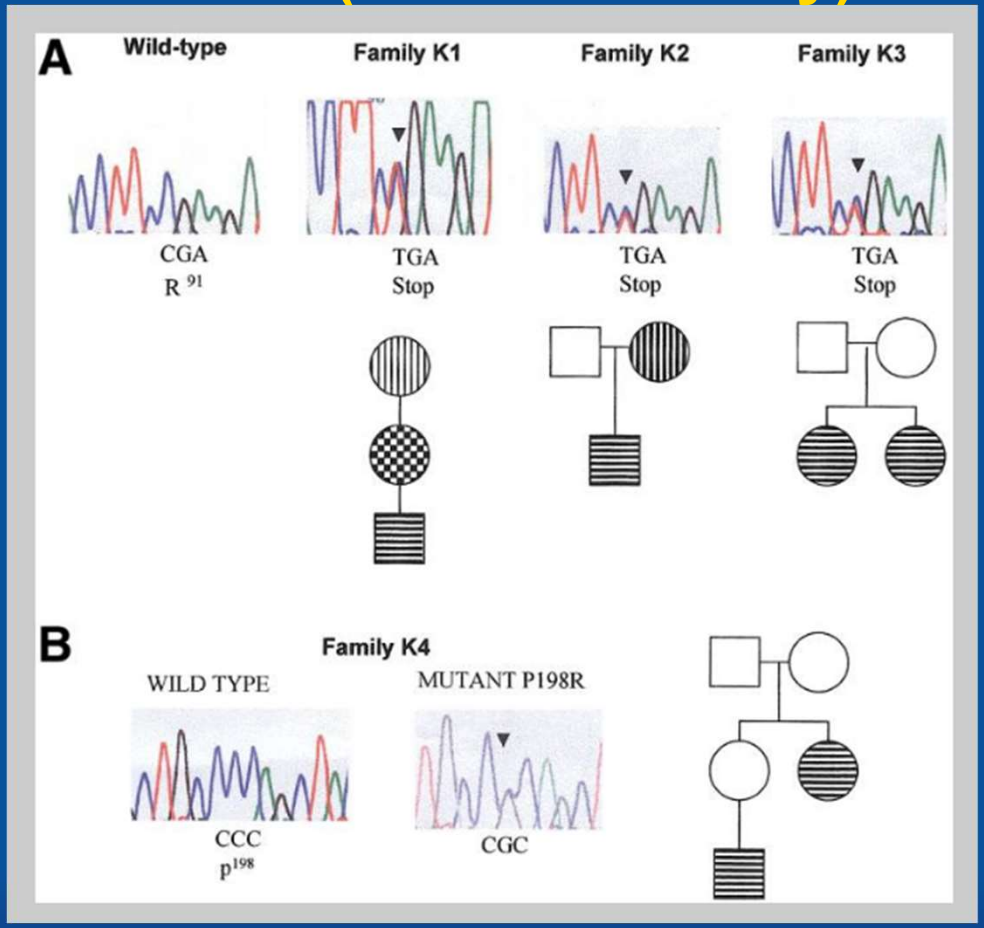
Human Molecular Genetics, 2010, Vol. 19, No. 15 **3011–3020**
doi:10.1093/hmg/ddq206
Advance Access published on May 18, 2010

SDHA is a tumor suppressor gene causing paraganglioma

Nelly Burnichon[1,2,3,*], Jean-Jacques Brière[4], Rossella Libé[3,5,6,7], Laure Vescovo[8], Julie Rivière[2,3], Frédérique Tissier[3,5,7,9], Elodie Jouanno[1], Xavier Jeunemaitre[1,2,3], Paule Bénit[10,11], Alexander Tzagoloff[4], Pierre Rustin[10,11], Jérôme Bertherat[3,5,6,7], Judith Favier[2,3] and Anne-Paule Gimenez-Roqueplo[1,2,3,7]



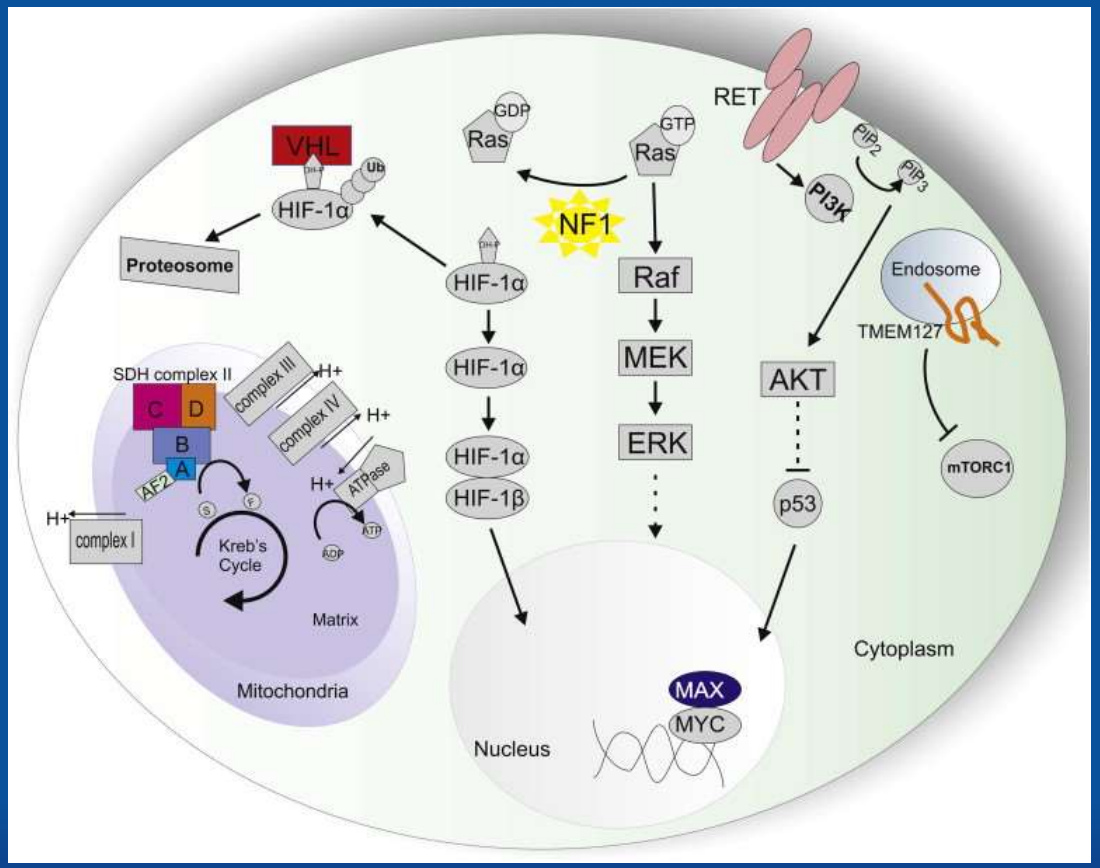
SDHB mutations (first discovery)



Astuti D, et al. Am. J. Hum. Genet. 69;49-54, 2001

Genetic testing in Pheo/Paraganglioma

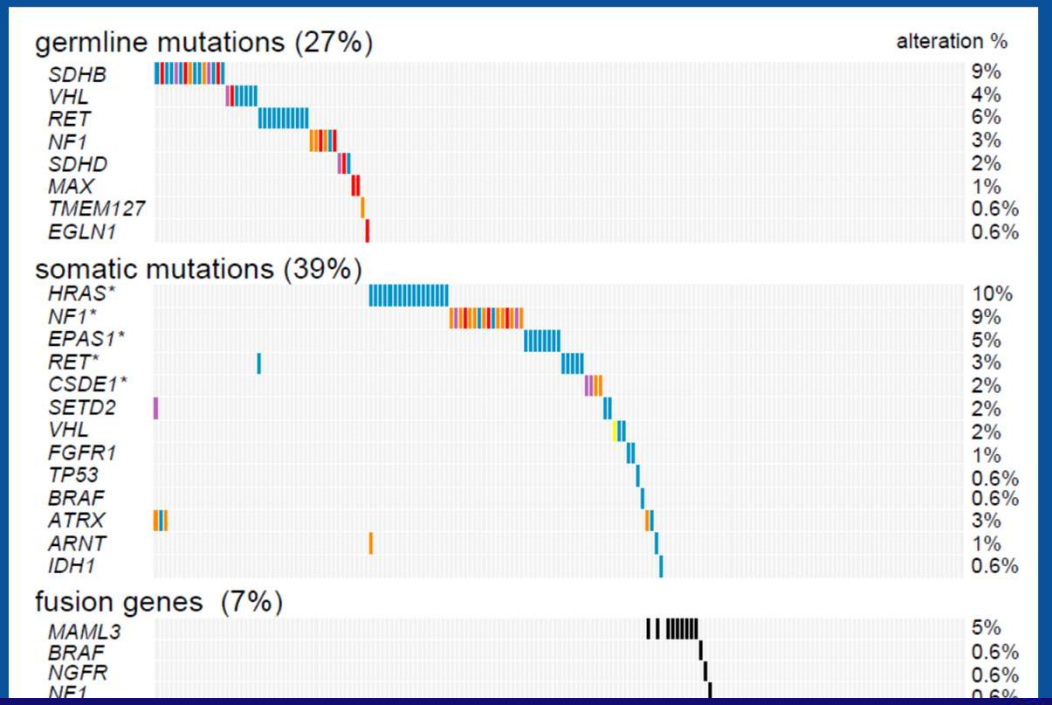
RET
NF1
VHL
SDHD
SDHB
SDHC
SDHA
SDHAF2
MAX
TMEM127
EPAS1
FH



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

TCGA data

25 Genes



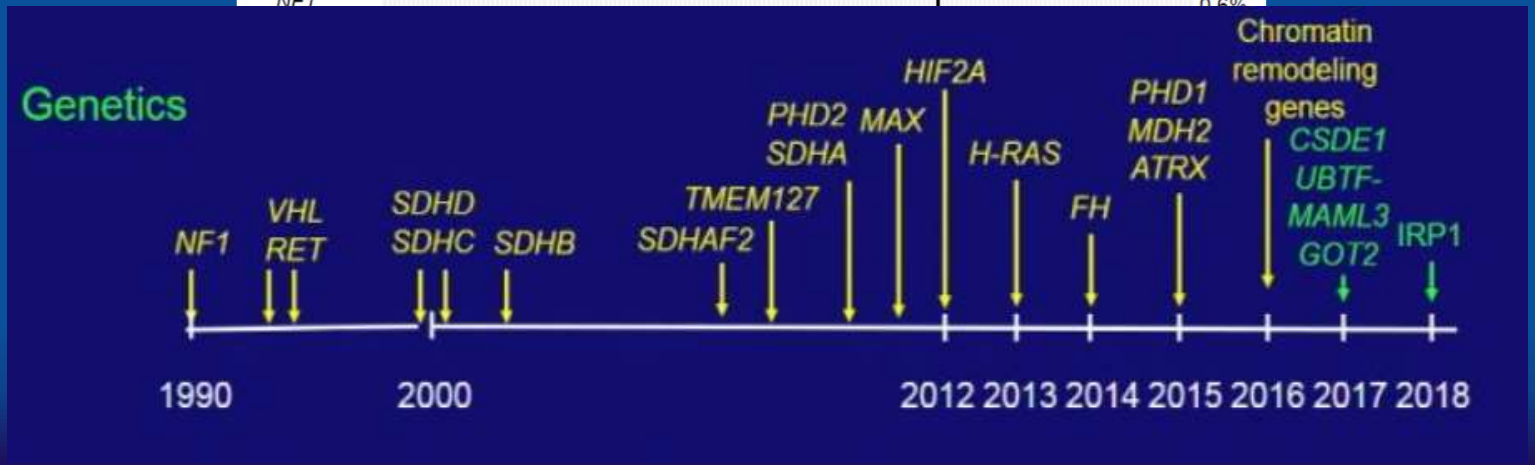


Table 1. Penetrance of cluster 1–related PPGLs

Penetrance	*SDHB*	*SDHA*	*SDHC*	*SDHD*	*VHL*
50 years	21%				
60 years	42% and 22%, respectively			43%	
80 years	25-65%				
Lifetime estimate	22%	1.7%	8.3%		15-20%

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 1 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.

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

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

Follow up of asymptomatic SDHx carriers

Adults

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

- Every 12 months
  - Clinical examination (BP)
  - Biochemical testing
- Every 24-36 months
  - MRI (Head-pelvis)
  - ? ^{68}Ga PET CT

Children

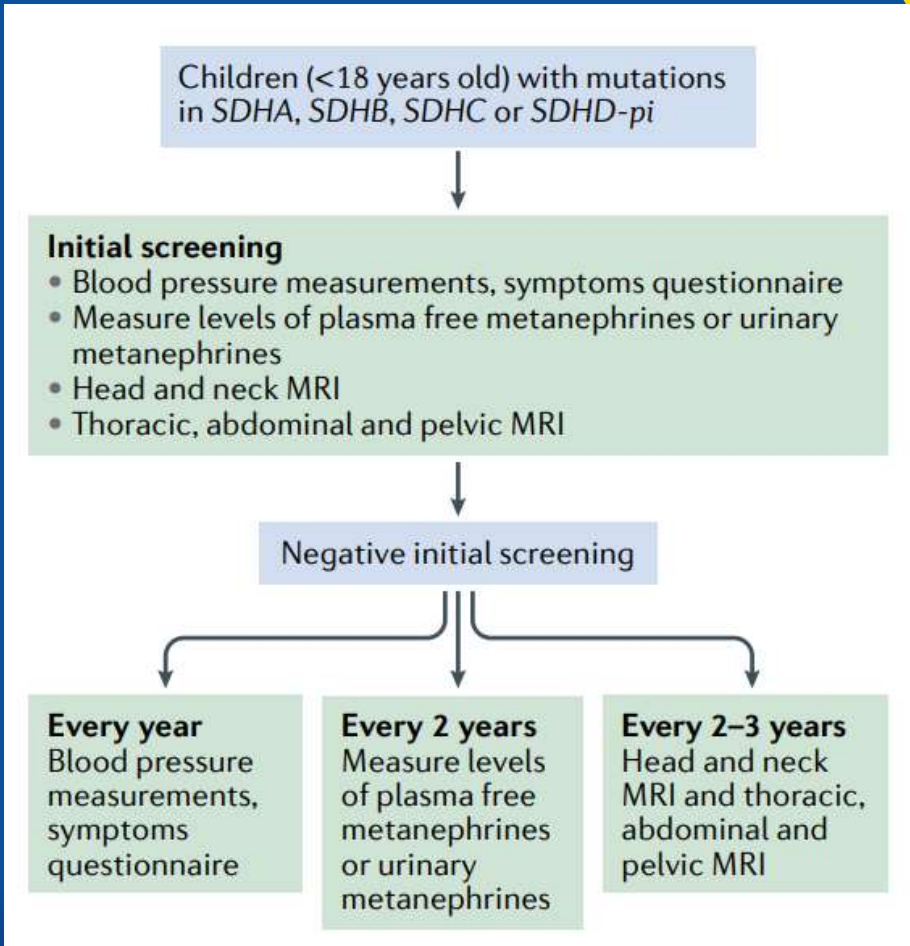
- Clinical examination (BP)
- Biochemical testing
- MRI (Head-pelvis)
- ~~^{68}Ga PET CT~~

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)

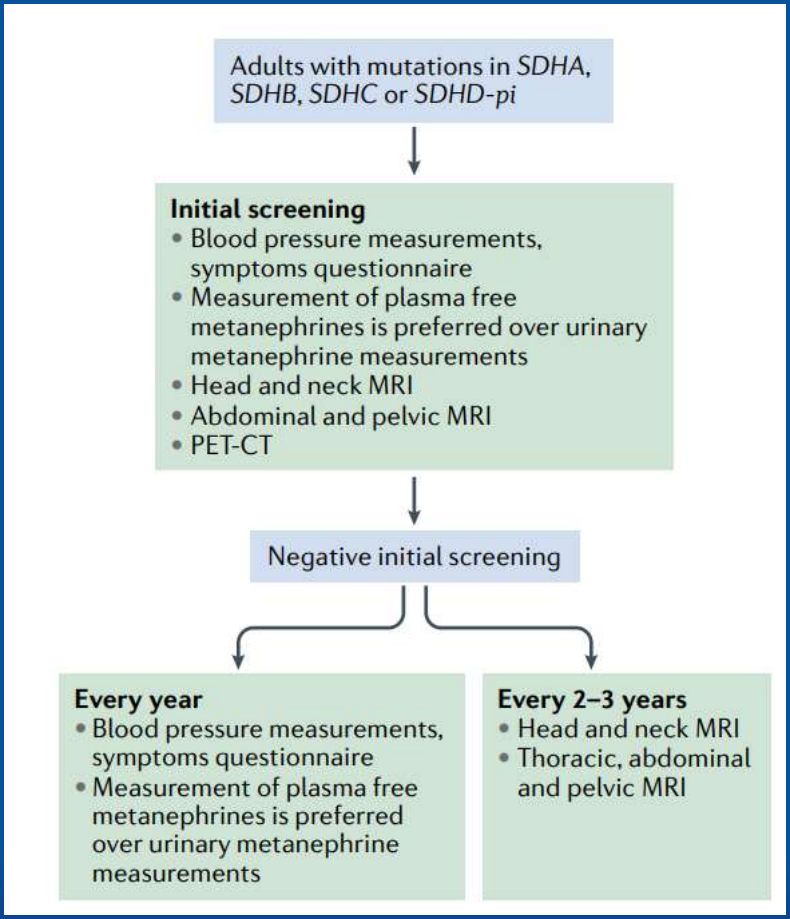
Nolting S, et al. Endocrine Reviews: 43:199–239, 2022

Management of SDHx mutation carriers (Children)



Amar L, et al, Nature Reviews Endocrinology;17:435-444, 2021

Management of SDHx mutation carriers (adults)



Amar L, et al, Nature Reviews Endocrinology;17:435-444, 2021

www.oncotarget.com Oncotarget, 2019, Vol. 10, (No. 57), pp: 5919-5931

Research Paper

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

Shatha Albattal[1,6], Meshael Alswailem[1], Yosra Moria[2], Hindi Al-Hindi[3], Majed Dasouki[4,5], Mohamed Abouelhoda[4,5], Hala Aba Alkhail[3], Entissar Alsuhaibani[6] and Ali S. Alzahrani[1,2]

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***Keywords:** pheochromocytoma; paraganglioma; mutations; NGS; SDHB*

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Clinical and pathological features

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

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

Albattal, S et al. Oncotarget, 2019, 10;5919-5931

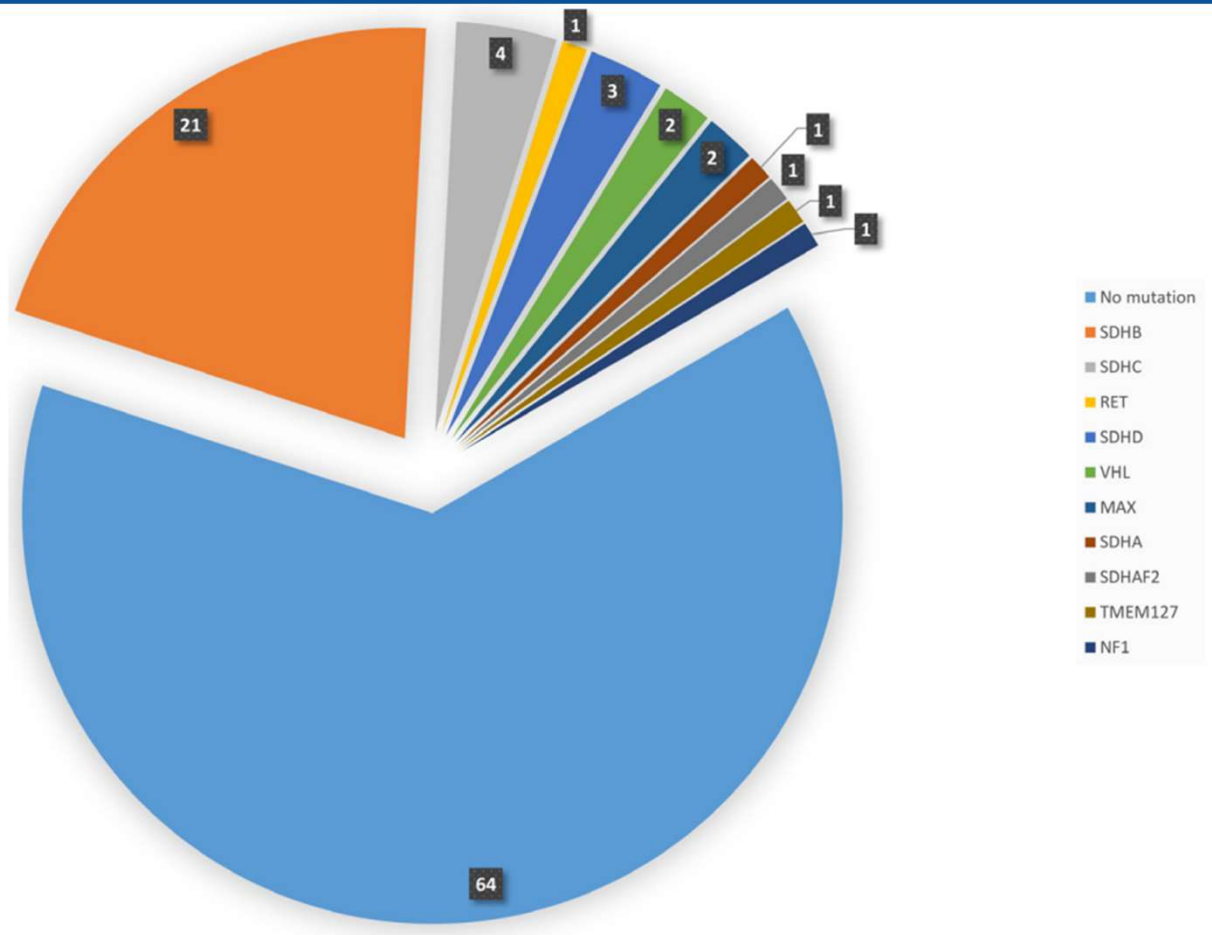


Figure 1: Pie diagram showing the distribution and number of cases with germline mutations in different gene.

Albattal S, et al. Oncotarget, 2019, 10;5919-5931

SDHB (p.R90X)

Endocrine
https://doi.org/10.1007/s12020-020-02461-8

ENDOCRINE GENETICS/EPIGENETICS

One genotype, many phenotypes: *SDHB* p.R90X mutation-associated paragangliomas

Ali S. Alzahrani[1,2] · Meshael Alswailem[2] · Yosra Moria[1] · Ayman Aldeheshi[3] · Hindi Al-Hindi[3]

Received: 20 June 2020 / Accepted: 8 August 2020

Features of 13 cases with *SDHB* R90* mutation

Table 1 Clinical and pathological characteristics, management, and outcome of 13 patients with *SDHB* p.R90X mutation-associated PPGL

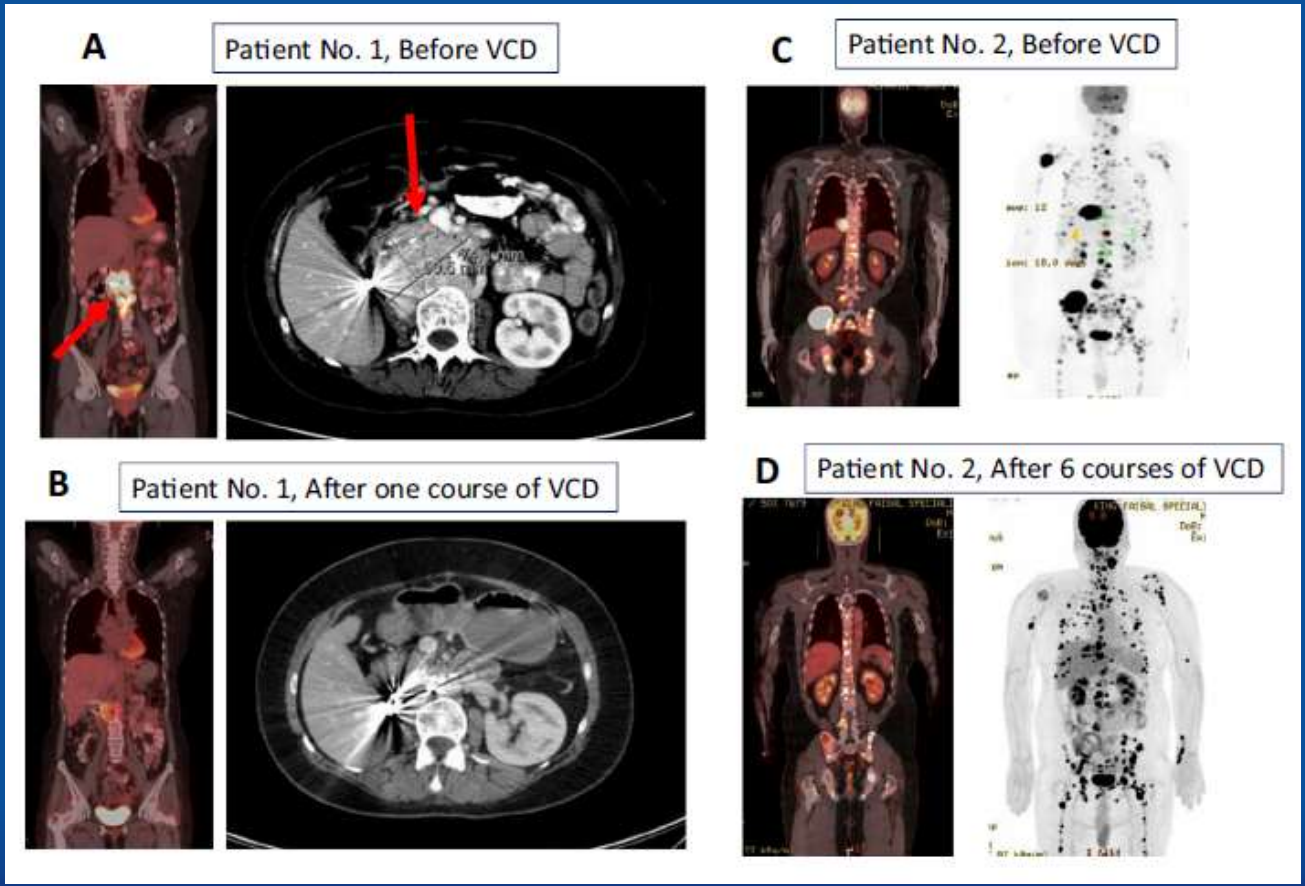
No.	Age at Dx	Sex	Family Hx	Location	Size (cm)	Distant Mets.	Initial Tx	Additional Tx	Outcome	Duration (years)
1	23	F	Yes	Abdomen	5	Yes	Sx	Sx, MIBG, VCD	Death	15
2	43	M	Yes	Abdomen	10	Yes	VCD	Pazopanib	Progression	1.8
3	24	M	Yes	Abdomen	12	Yes	VCD	Lu^{177}, Sorafenib	Death	4
4	24	M	Yes	Abdomen	13	Yes	Sx	MIBG, XRT	Progression	14
5	36	M	No	Abdomen and head	18	Yes	Sx	MIBG, XRT	Death	6
6	21	M	No	Abdomen	10	Yes	Sx		Death	4
7	23	F	No	Abdomen	7	No	Sx		Recurrence	10
8	10	F	No	Abdomen	4.5	No	Sx		Remission	7
9	21	F	No	Adrenal	4	No	Sx		Remission	4
10	23	M	No	Neck (carotid)	4.5	No	Sx		Remission	10
11	8	F	No	Abdomen	3	No	Sx		Remission	3
12	17	M	No	Abdomen	14	No	Sx		Remission	6
13	13	M	No	Abdomen	13	No	Sx		Remission	9

Mets Metastasis, *Tx* Therapy, *Sx* Surgery, *MIBG* Meta-iodobenzylguanidine, *VCD* vincristine, cyclophosphamide, and doxorubicin, *Lu177*; Lutetium 177, *XRT* External radiotherapy

Alzahrani A, et al. Endocrine, 2020 Dec;70(3):644-650

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

One genotype, multiple phenotypes

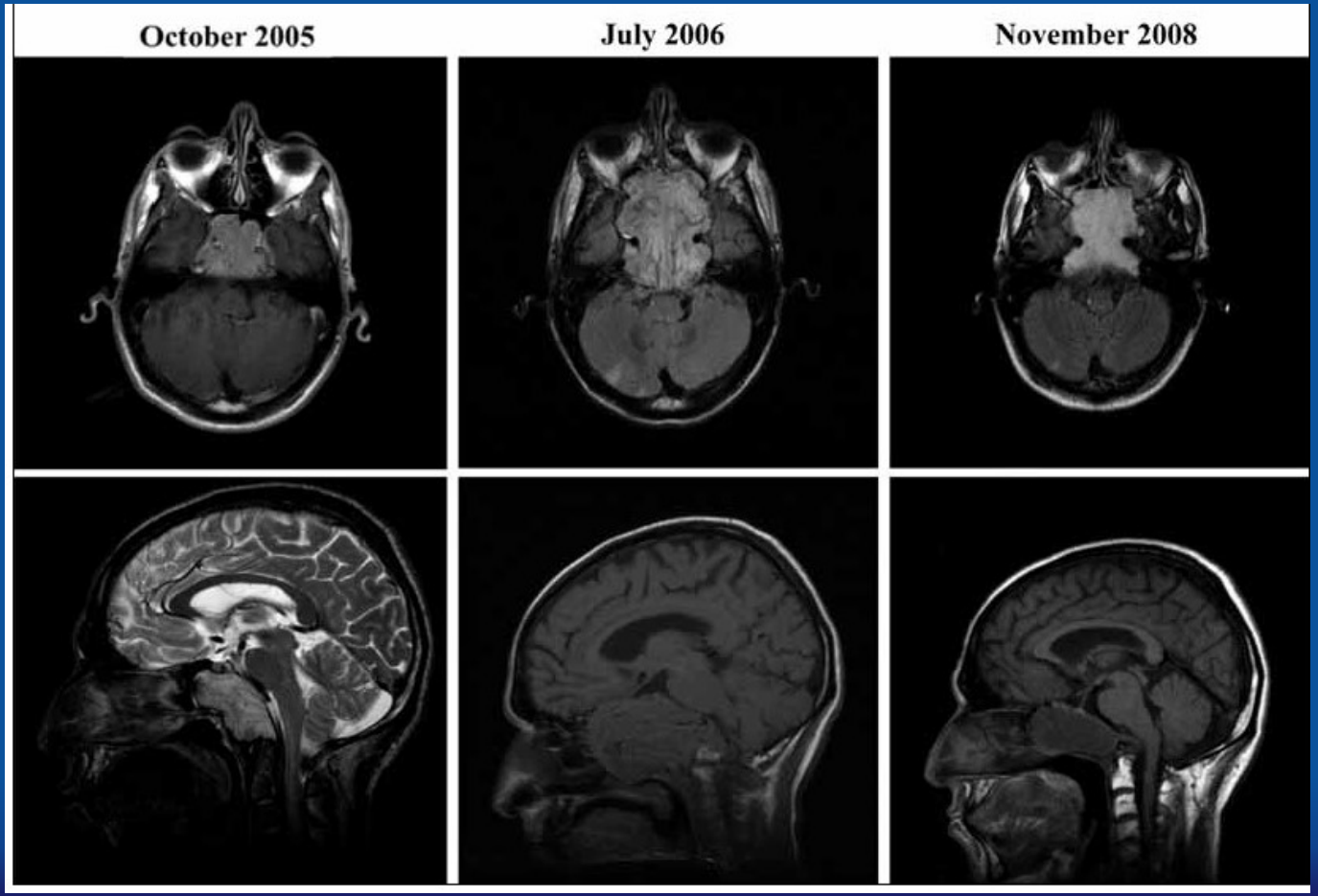


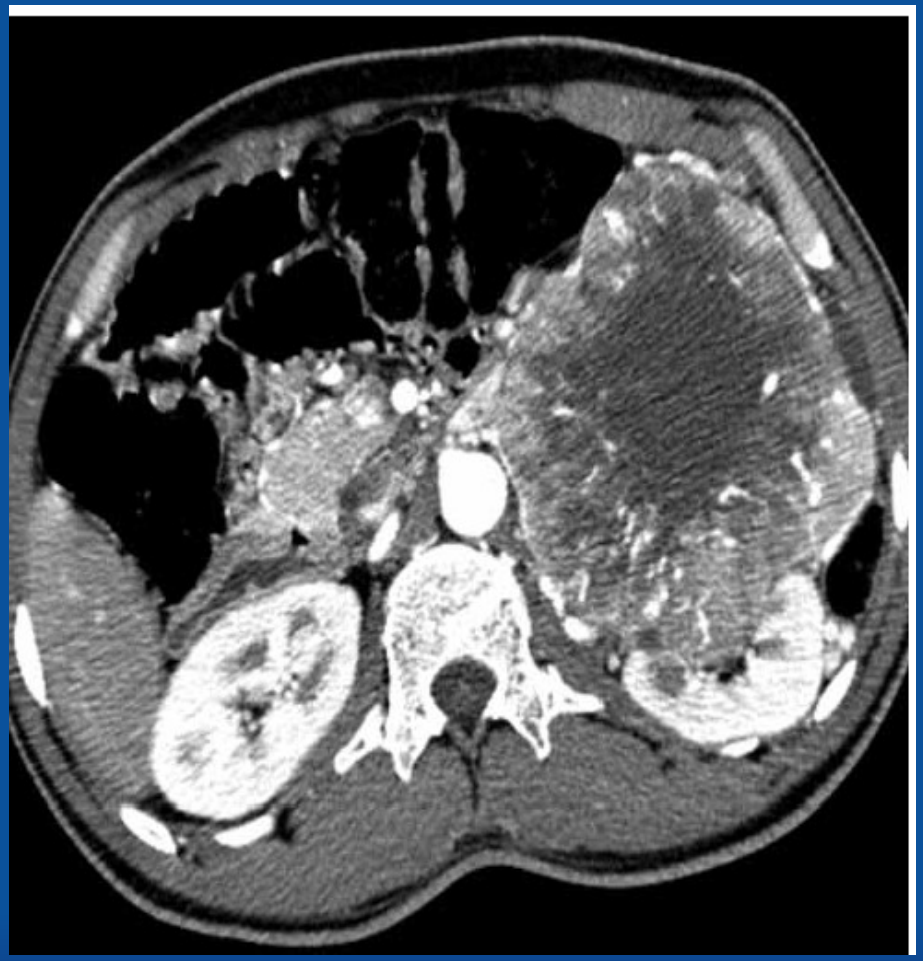
Alzahrani A, et al. Endocrine, 2020 Dec;70(3):644-650

Face 2: unusual location of SDHB-related PGL mesquarding as NP cancer or pituitary adenoma

Case 1

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



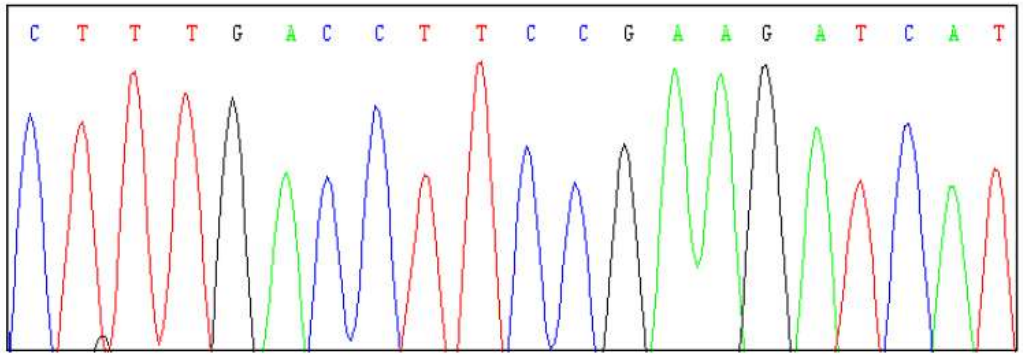


Alzahrani A, et al, Endocrine Practice 16(3):452-8

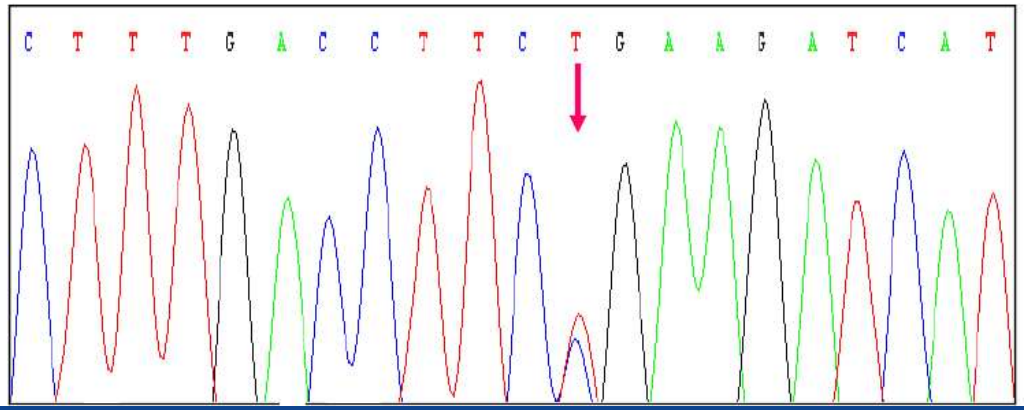
MULTIPLE PARAGANGLIOMA SYNDROME TYPE 4 DUE TO SUCCINATE DEHYDROGENASE B MUTATION: DIAGNOSTIC AND THERAPEUTIC CHALLENGES OF A SKULL BASE PARAGANGLIOMA MASQUERADING AS NASOPHARYNGEAL CANCER

Ali S. Alzahrani, MD, FACE[1]; Omalkhaire Alshaikh, MD[1]; Muhammad Faiyaz-Ul-Haque, PhD[2]; Halah Abalkhail, PhD[2]; Fouad Al-Dayel, MD[2]; Hindi Al Hindi, MD[2]

SDHB-Normal



SDHB-R90X Mutation



Alzahrani A, et al, Endocrine Practice 16(3):452-8

Face 3: Primary hyperparathyroidism and thyroid cancer in a patient with multiple PGL and SDHB mutation
Variable penetrance within the same family

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 Alswailem[2], Shatha Albatal[2], Ebtesam Qasem[2], Avanyapuram K Murugan[2] & Hindi Al-Hindi[3]

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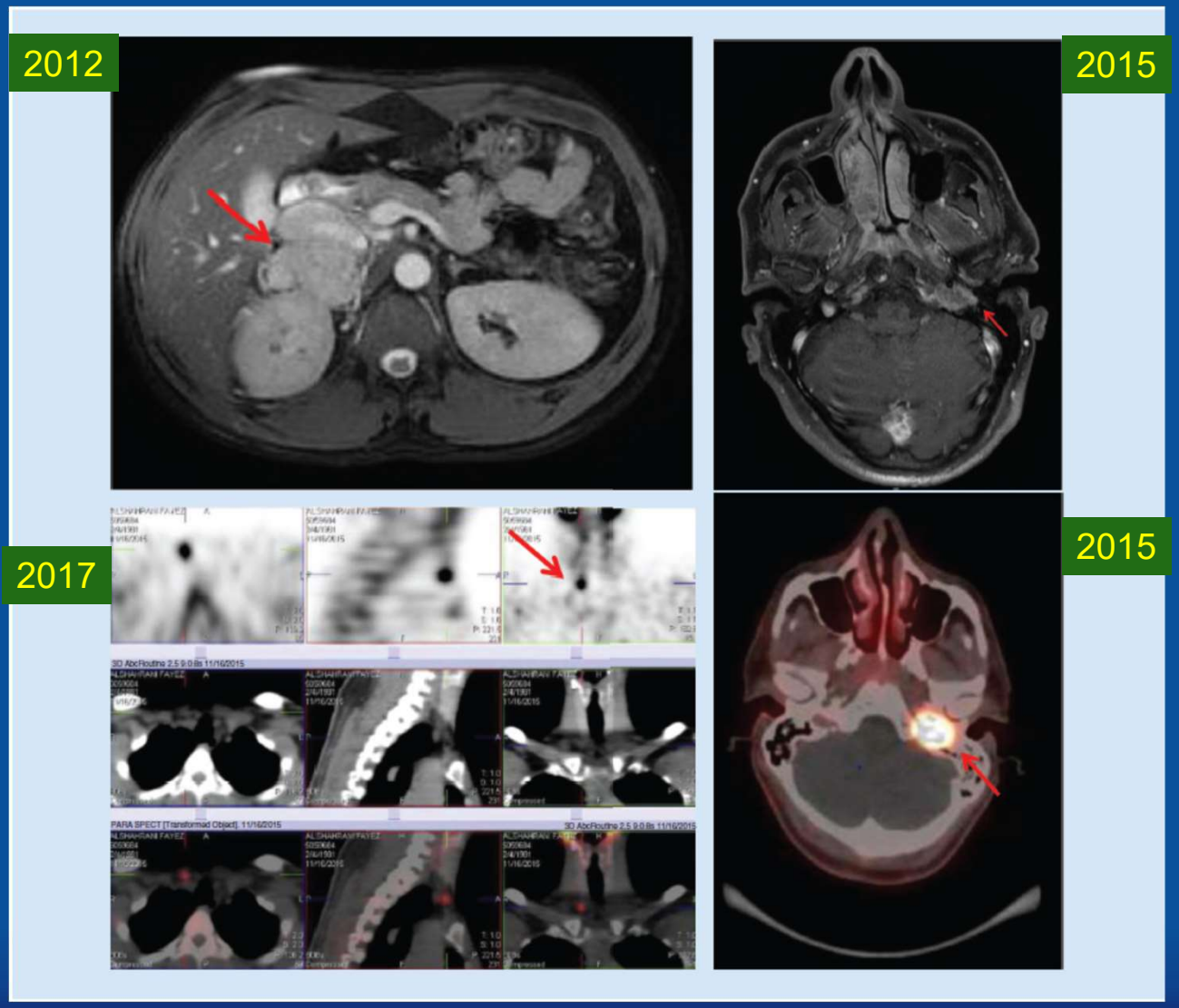
[2]Department of Molecular Oncology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia
[3]Department of Pathology & Laboratory Medicine, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia
*Author for correspondence: aliz@kfshrc.edu.sa

International Journal of Endocrine Oncology

Alzahrani A, et al, International Journal of Endocrine Oncology, Vol. 6, No. 1 |



Alzahrani A, et al, International Journal of Endocrine Oncology, Vol. 6,

A novel *SDHB* mutation (c.409A>G, p.K137E)

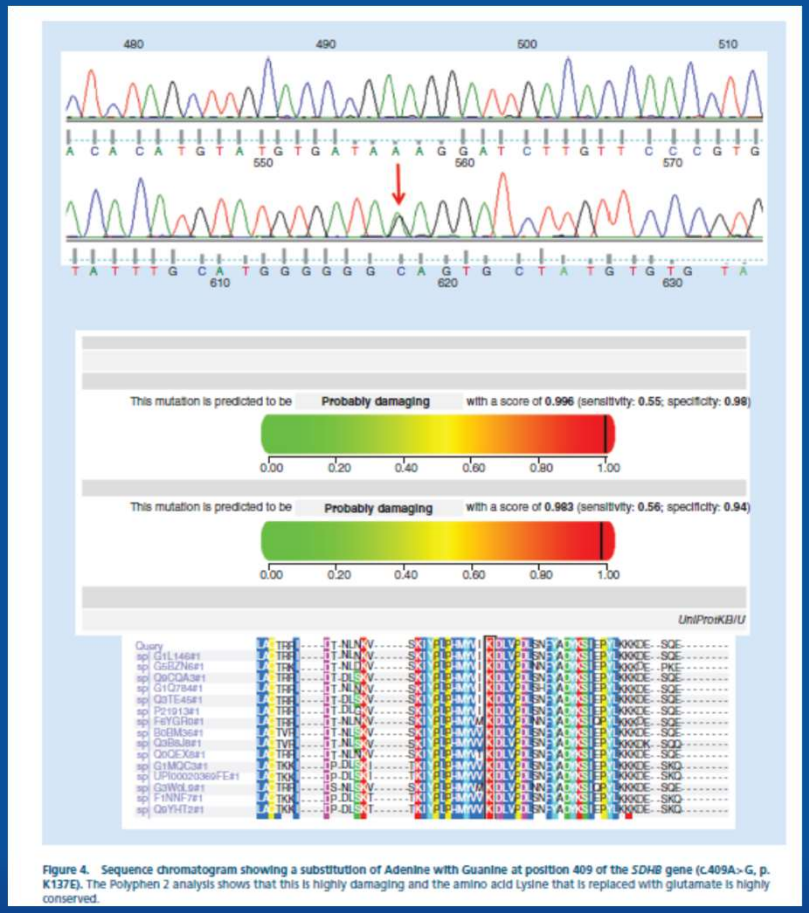
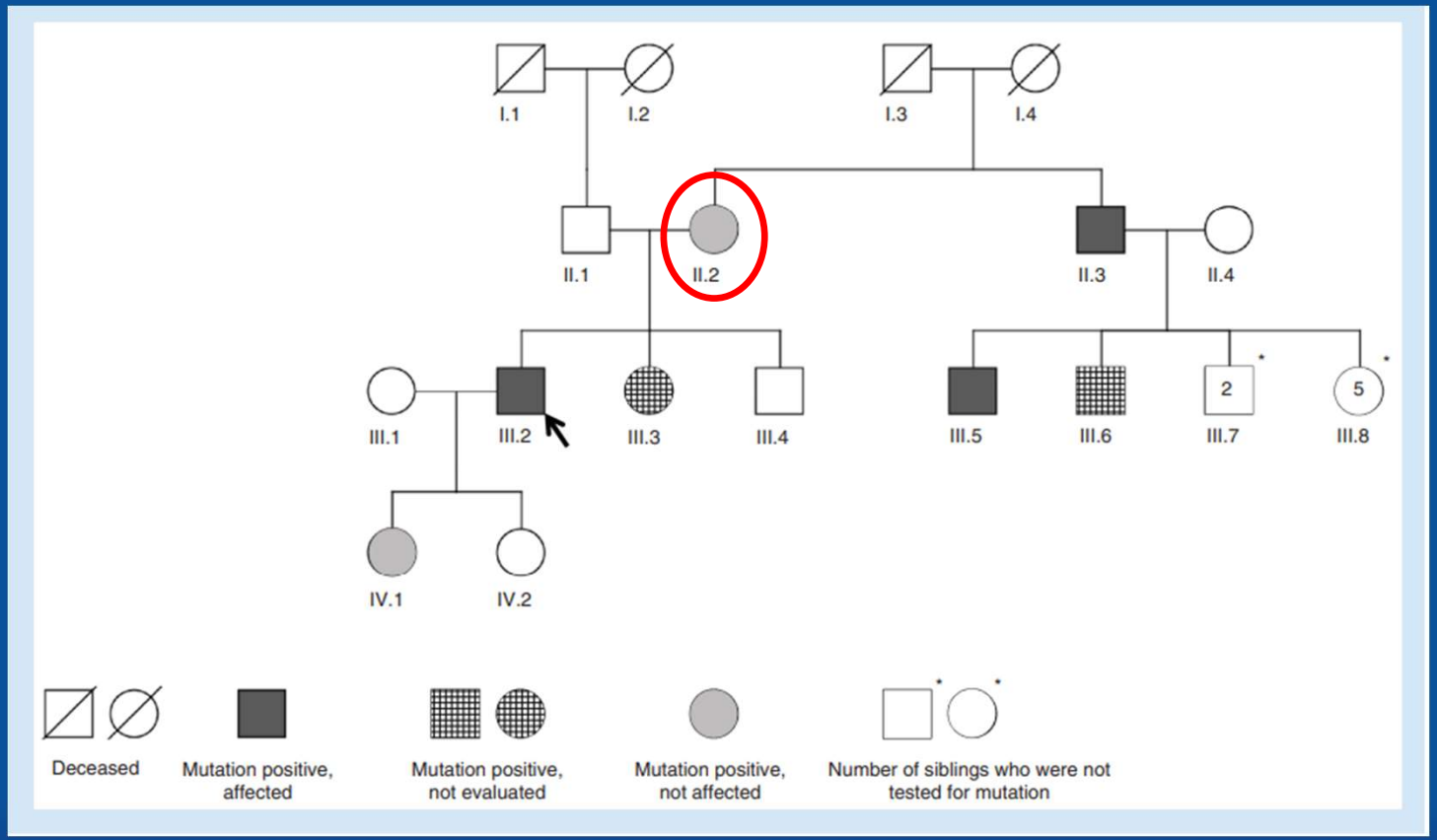
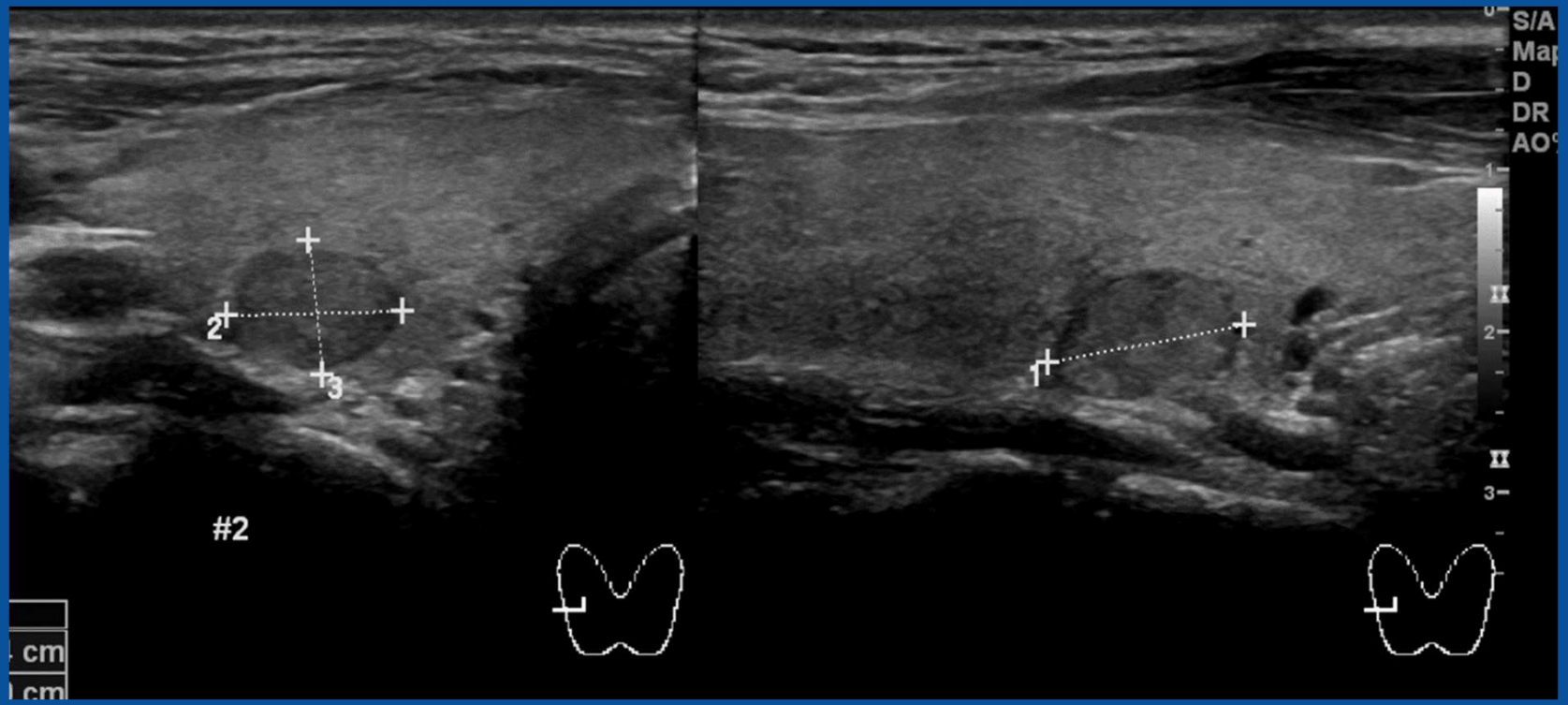


Figure 4. Sequence chromatogram showing a substitution of Adenine with Guanine at position 409 of the *SDHB* gene (c.409A>G, p. K137E). The Polyphen 2 analysis shows that this is highly damaging and the amino acid Lysine that is replaced with glutamate is highly conserved.

Alzahrani A, et al, International Journal of Endocrine Oncology, Vol. 6,


I.1
I.2
I.3
I.4
II.1
II.2
II.3
II.4
III.1
III.2
III.3
III.4
III.5
III.6
2
III.7
5
III.8
IV.1
IV.2
Deceased
Mutation positive, affected
Mutation positive, not evaluated
Mutation positive, not affected
Number of siblings who were not tested for mutation

July 2023



FNA: Papillary thyroid cancer

Total thyroidectomy: 1.4 cm PTC with 4 vessel angioinvasion

Is thyroid cancer related to SDHB?

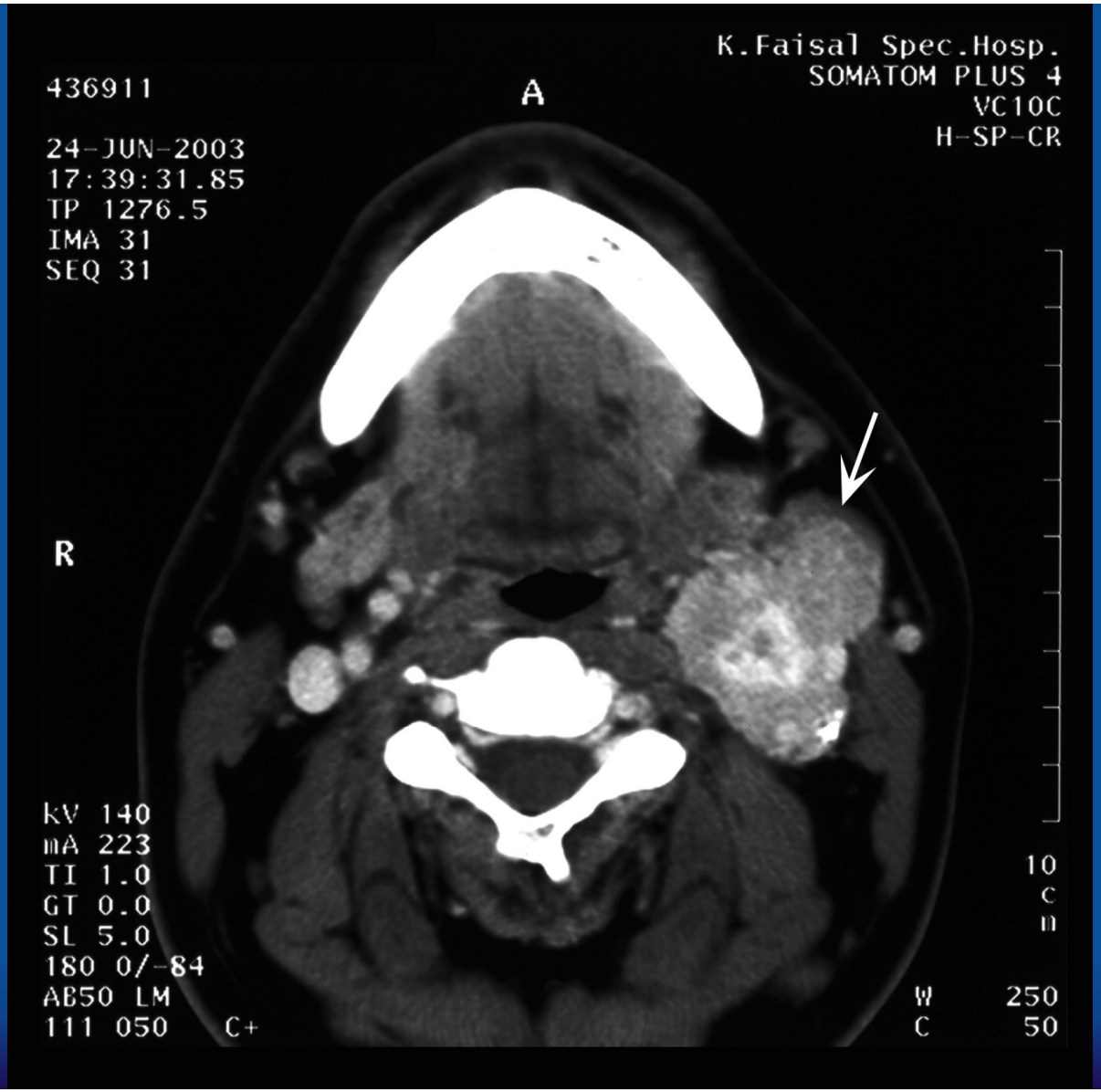
Face 4: Living most of his life with persistent and recurrent PGL + polycythemia

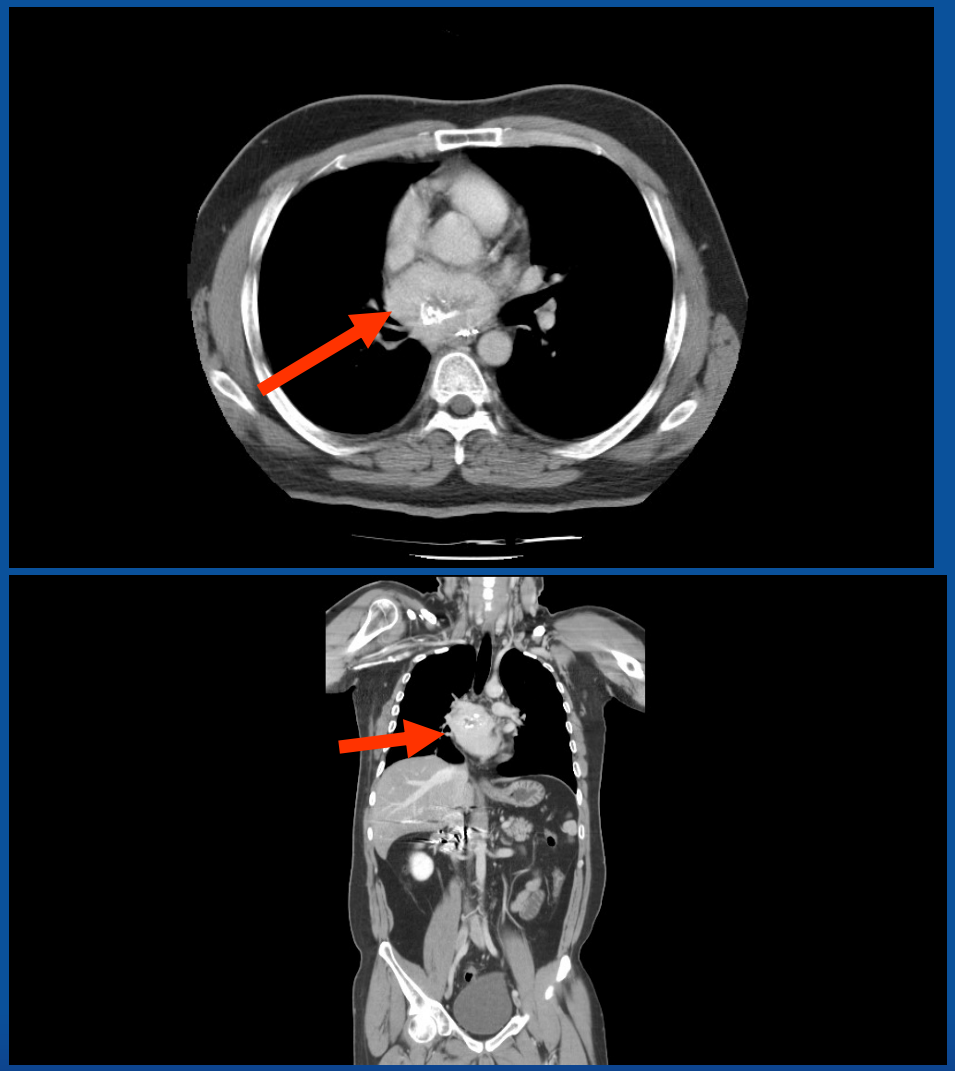
Case 3

A 56-year old man

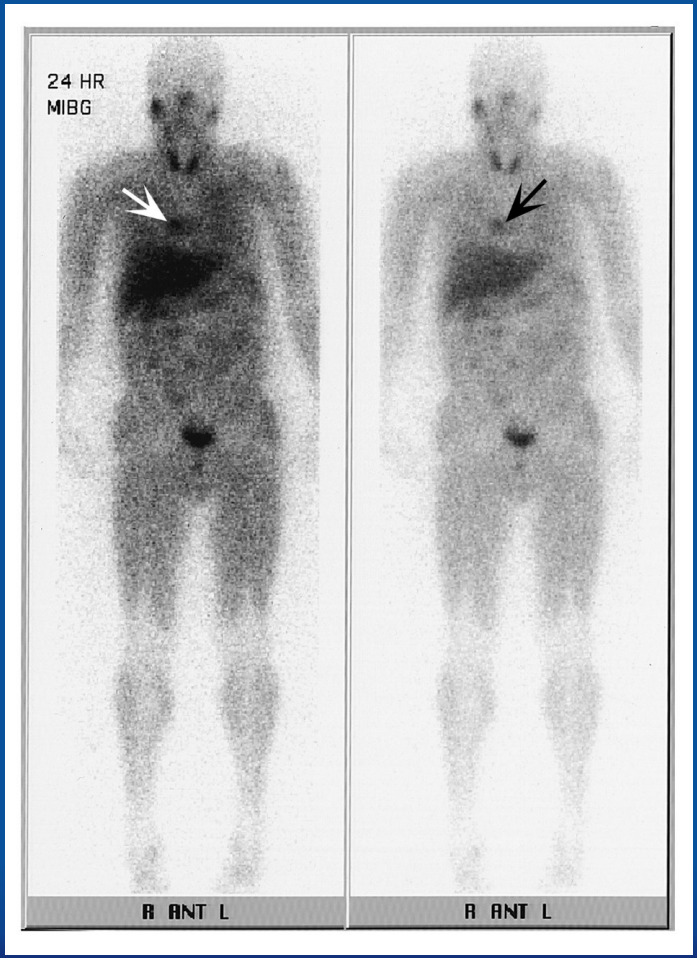
Multiple para/pheo

- Pheo at age 20 yrs
- Mediastinal PGL at age 32 yrs
- Carotid body tumor at age 36 yrs


K.Faisal Spec.Hosp.
SOMATOM PLUS 4
VC10C
H-SP-CR
436911
A
24-JUN-2003
17:39:31.85
TP 1276.5
IMA 31
SEQ 31
R
kV 140
mA 223
TI 1.0
GT 0.0
SL 5.0
180 0/-84
AB50 LM
111 050 C+
10
c
m
W 250
C 50



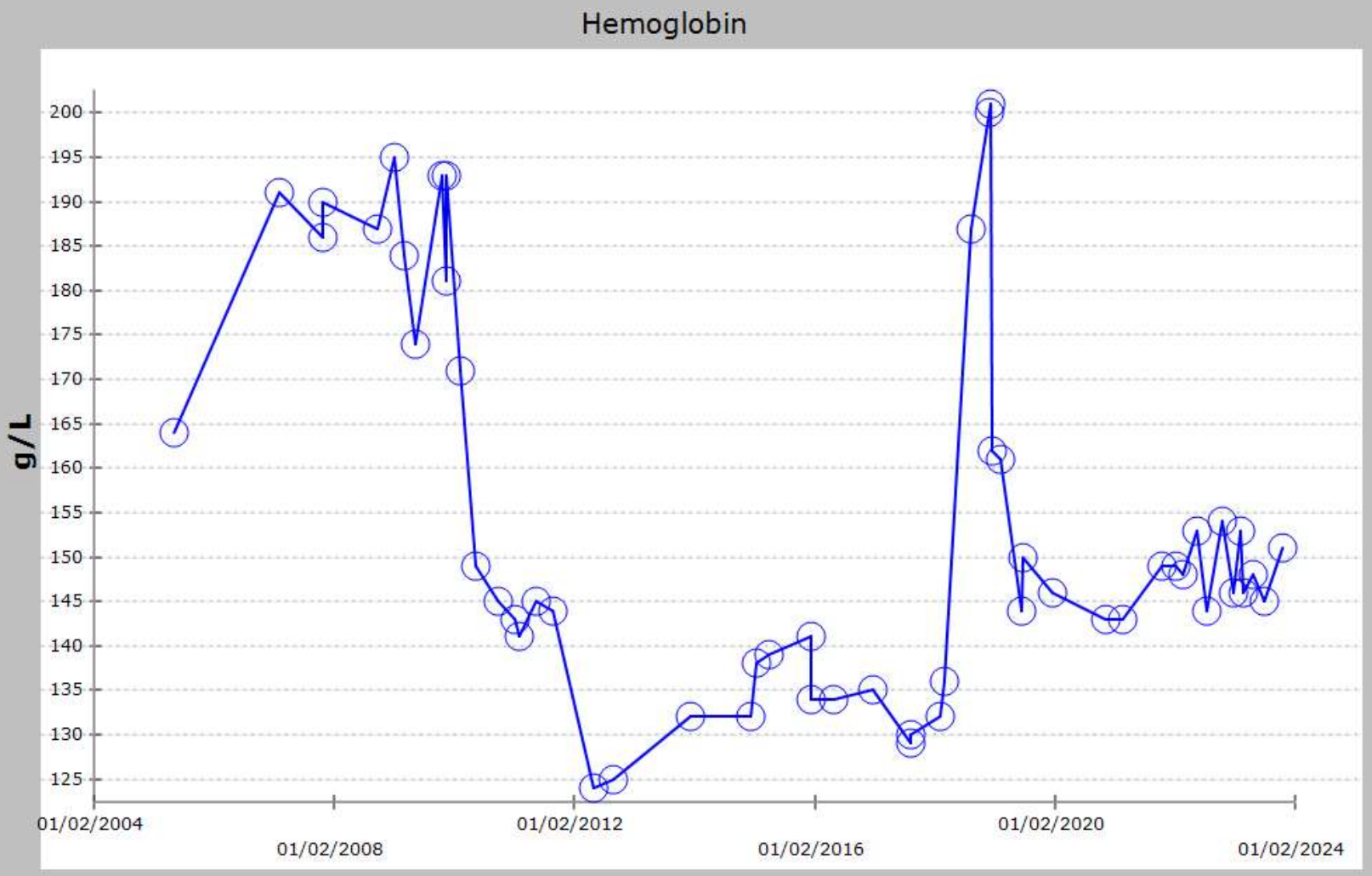
MIBG scan



SDHB:c.689G>A, p.Arg230His

1. **PRIMARY FINDINGS**

Gene / Variant	Genotype	ACMG Classification	Mode of Inheritance	Phenotype
SDHB c.689G>A p.Arg230His chr1:17349179:C>T	Heterozygous	Pathogenic	Dominant	Paragangliomas 4, OMIM# 115310 (3), Autosomal dominant; Pheochromocytoma, OMIM# 171300 (3), Autosomal dominant; Paraganglioma and gastric stromal sarcoma, OMIM# 606864 (3)



Is polycythemia related to *SDHB* variant, PGL or coincidental?

Face 4: an aggressive pituitary adenoma due to an SDHB mutation in the absence of PPGL

Case 4

An aggressive cabergoline-resistant, temozolomide-responsive macroprolactinoma 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]

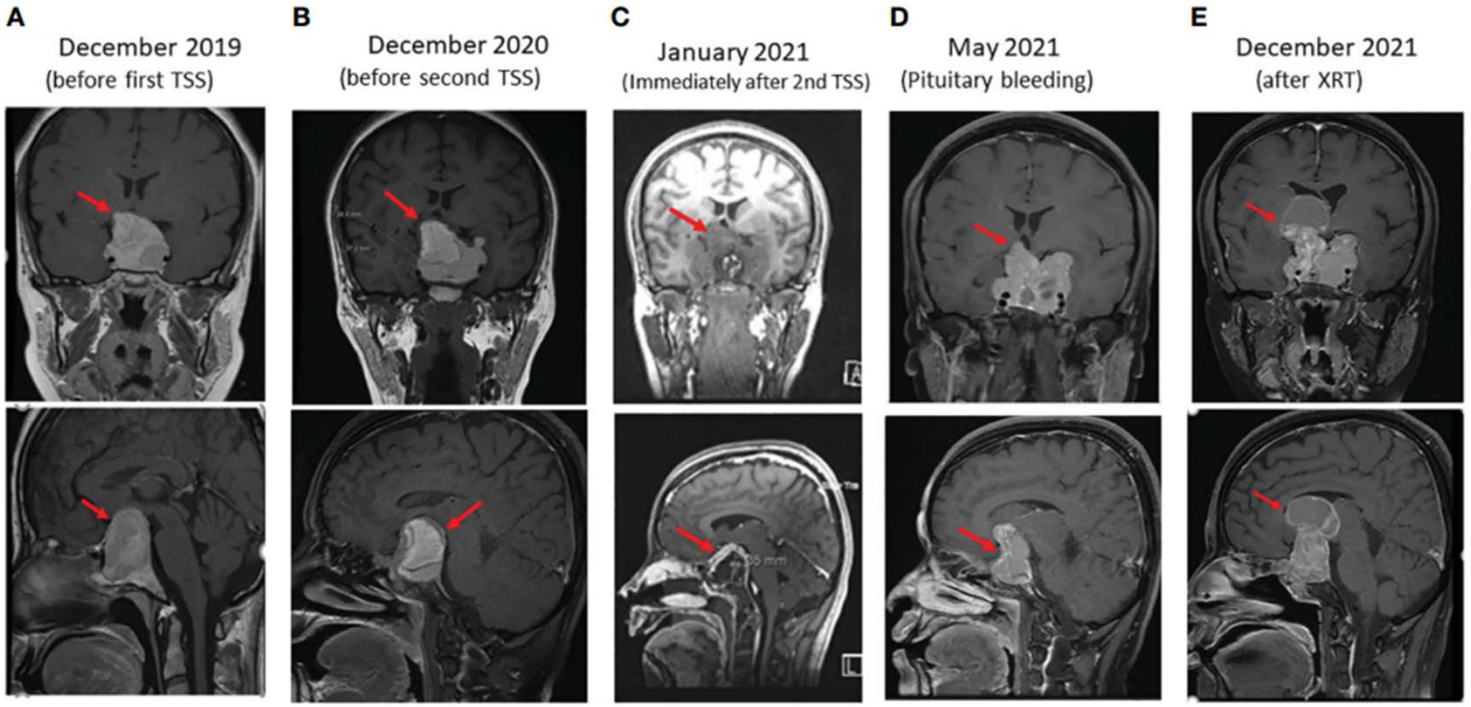


FIGURE 1
Sequential coronal (upper panels) and sagittal (lower panels) enhanced T1 weighted MR Images of macroprolactinoma at several stages (arrows) as follows: **(A)** before first trans sphenoidal surgery (TSS), **(B)** before second TSS, **(C)** immediately after Second surgery, **(D)** 4 months after second TSS presenting with bleeding in PA, and **(E)** 4 months after XRT.

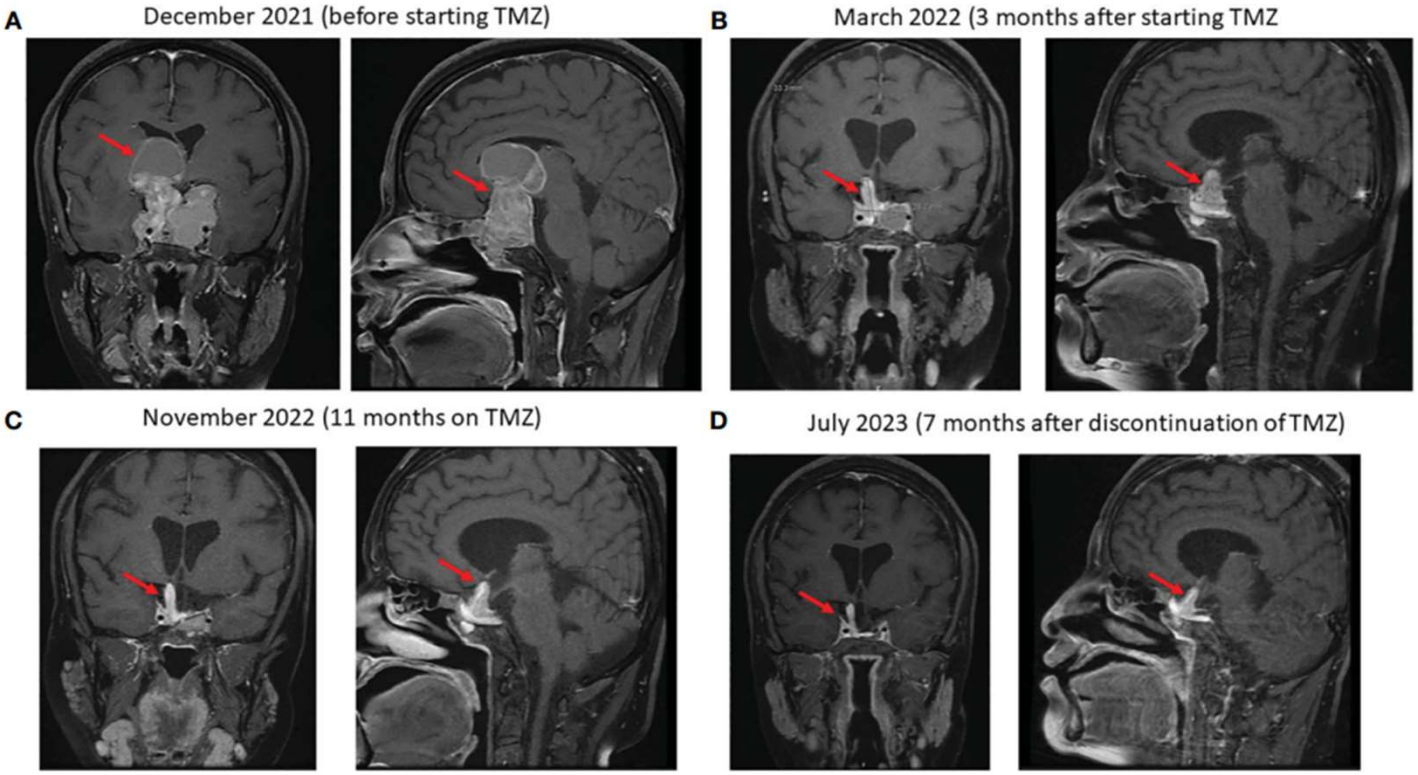


FIGURE 3
Sequential coronal and sagittal enhanced T1-weighted MR images showing the changes in the size of the macroprolactinoma (arrows) after starting temozolomide (TMZ): **(A)** at baseline just before starting TMZ, **(B)** 4 months later, **(C)** after 11 months on TMZ and **(D)** 7 months after discontinuation of TMZ.

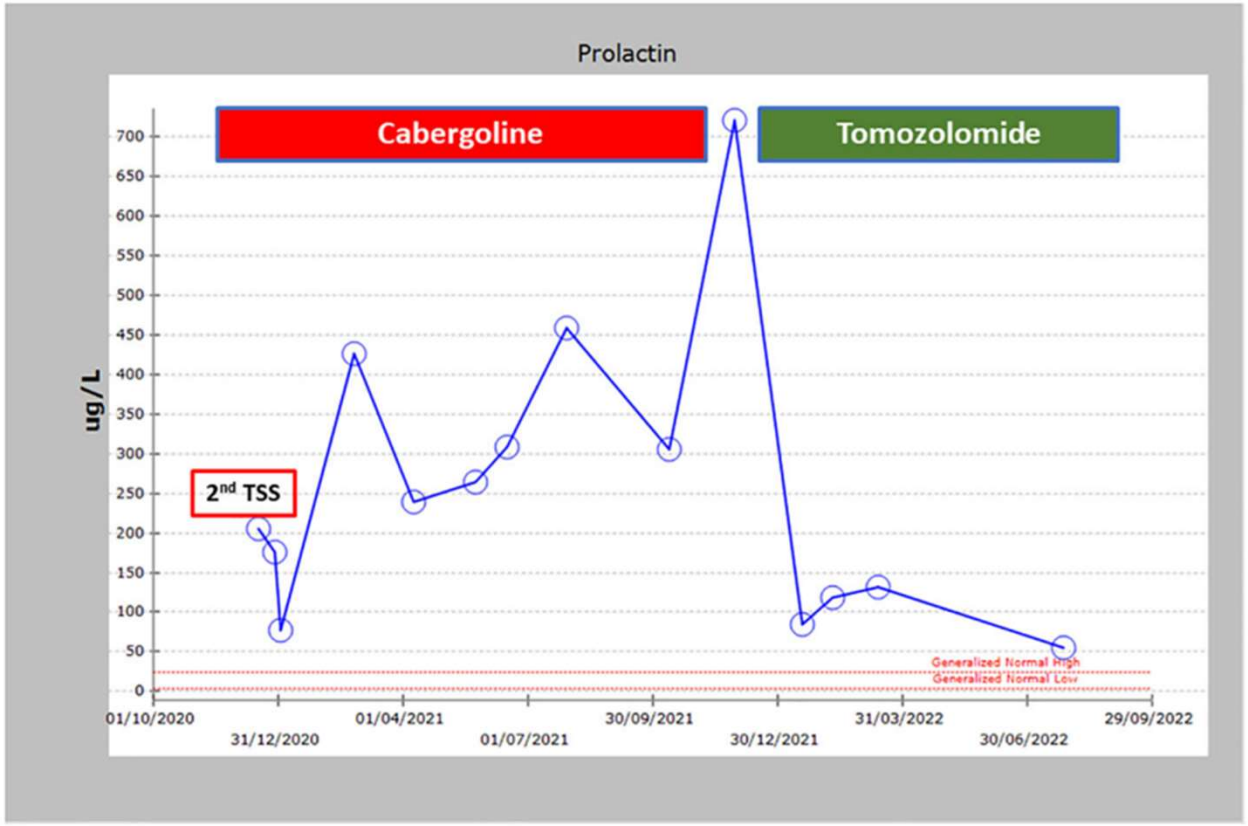


FIGURE 4
Prolactin levels over time showing the non-response to cabergoline and trans sphenoidal surgery and the dramatic response to TMZ.

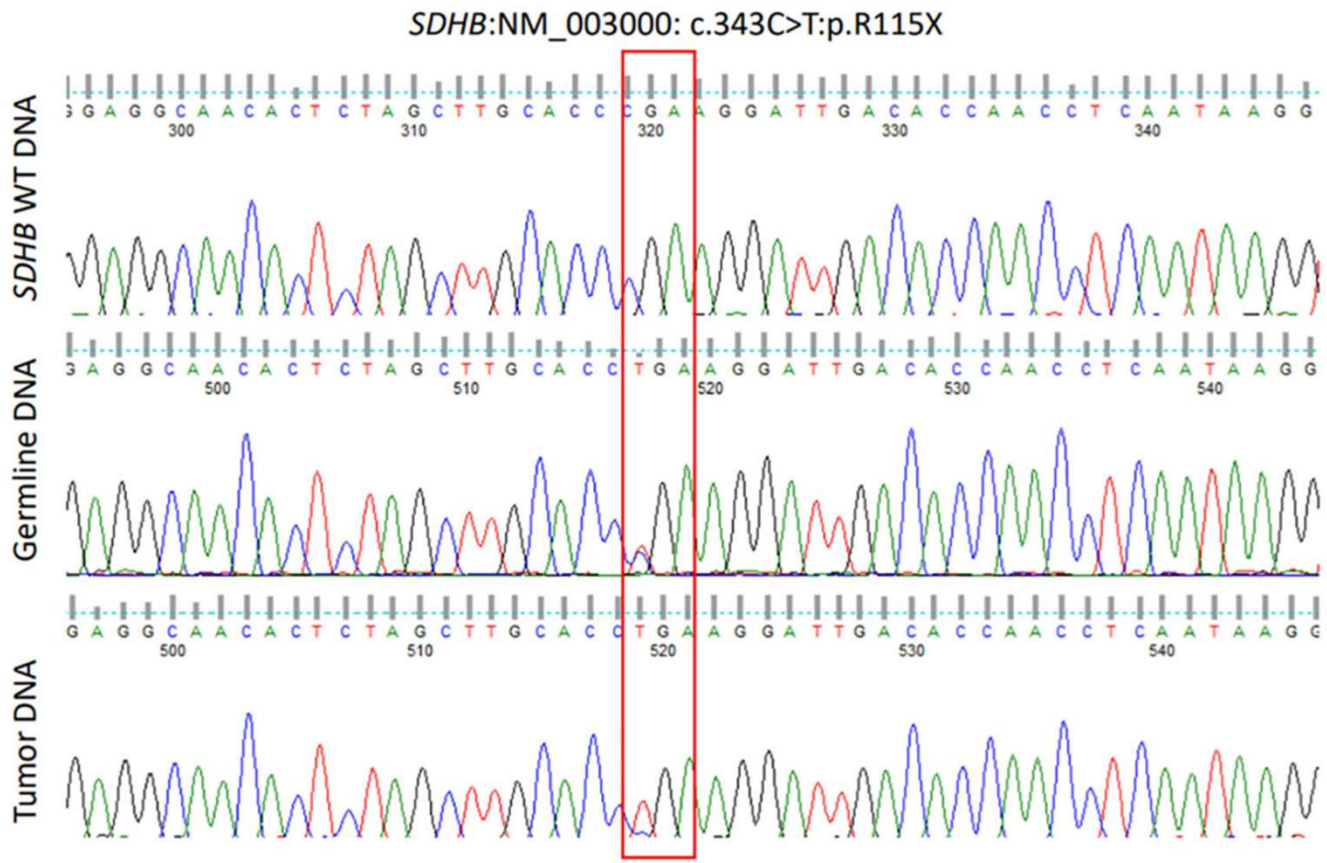


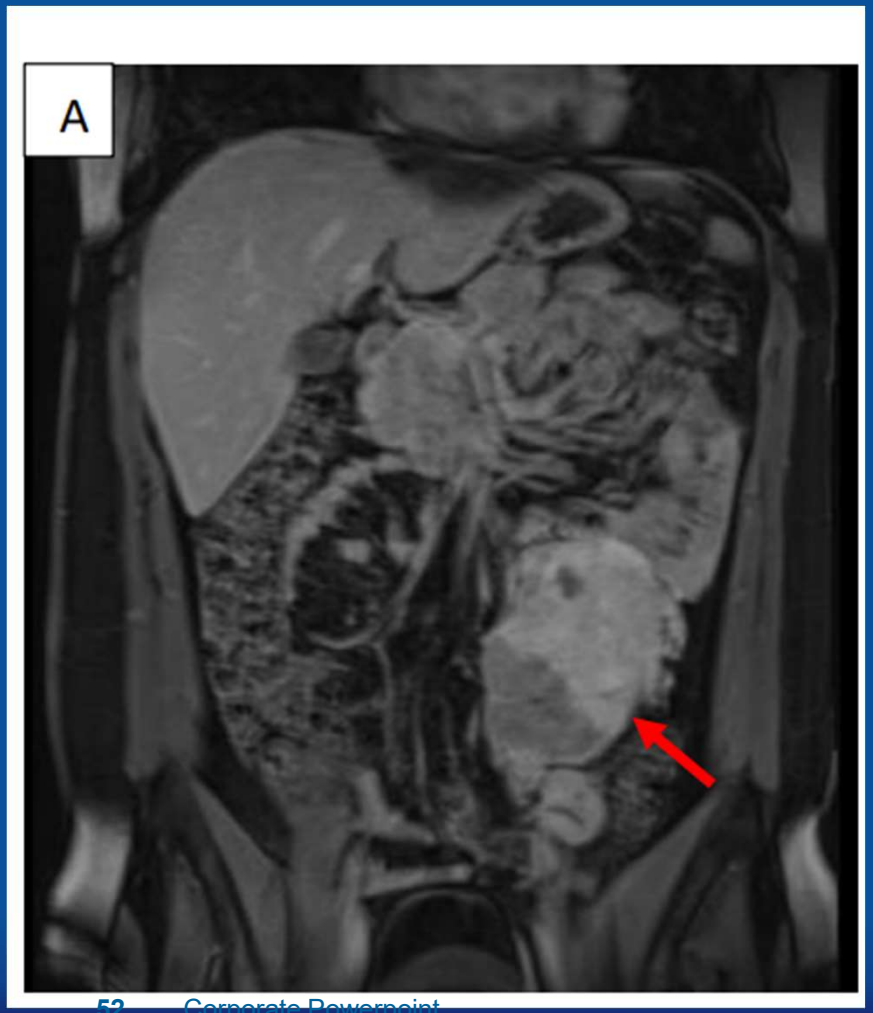
FIGURE 5
Chromatograms of part of *SDHB* exon 4 showing wild type sequence (upper panel), leucocyte DNA sequence (middle panel) showing a heterozygous germline mutation (NM_003000, c.343C>T) and pituitary adenoma (somatic) DNA sequence (lower panel) showing the same mutation in a homozygous form (loss of heterozygosity).

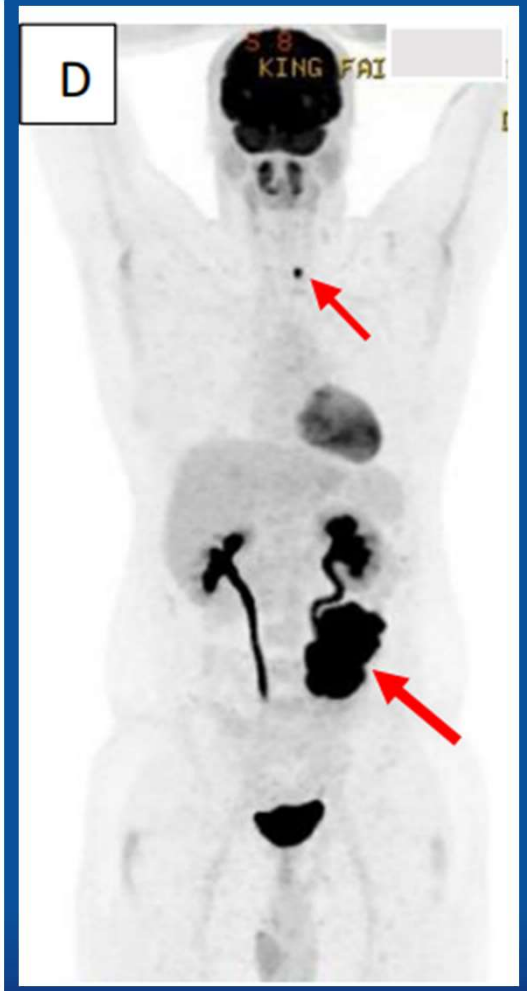
Face 5: metastatic PGL and thyroid cancer with an interesting combination of mutations

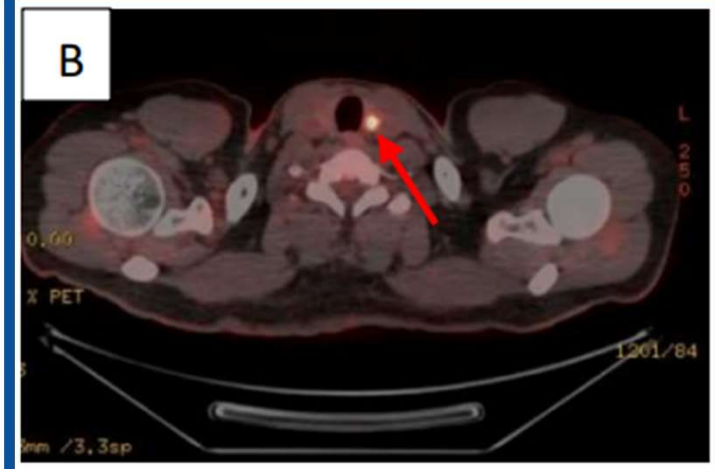
Case 5

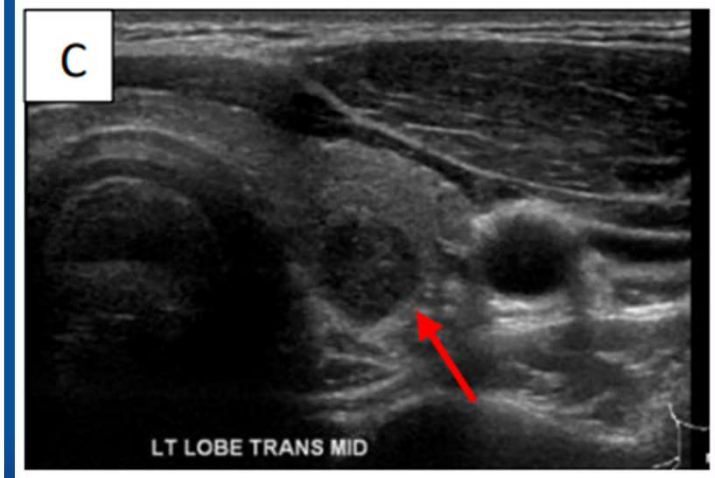
- AA was a 28-year old man without family history of PPGL
- Had varicocele in 2017 (surgically treated)
- Recurrent varicolcele 2019
- CT scan of the abdomen: a large mass 12x8x6.5 cm
- No symptoms at all.
- Urine metanephrines: normal x 3

September 2019

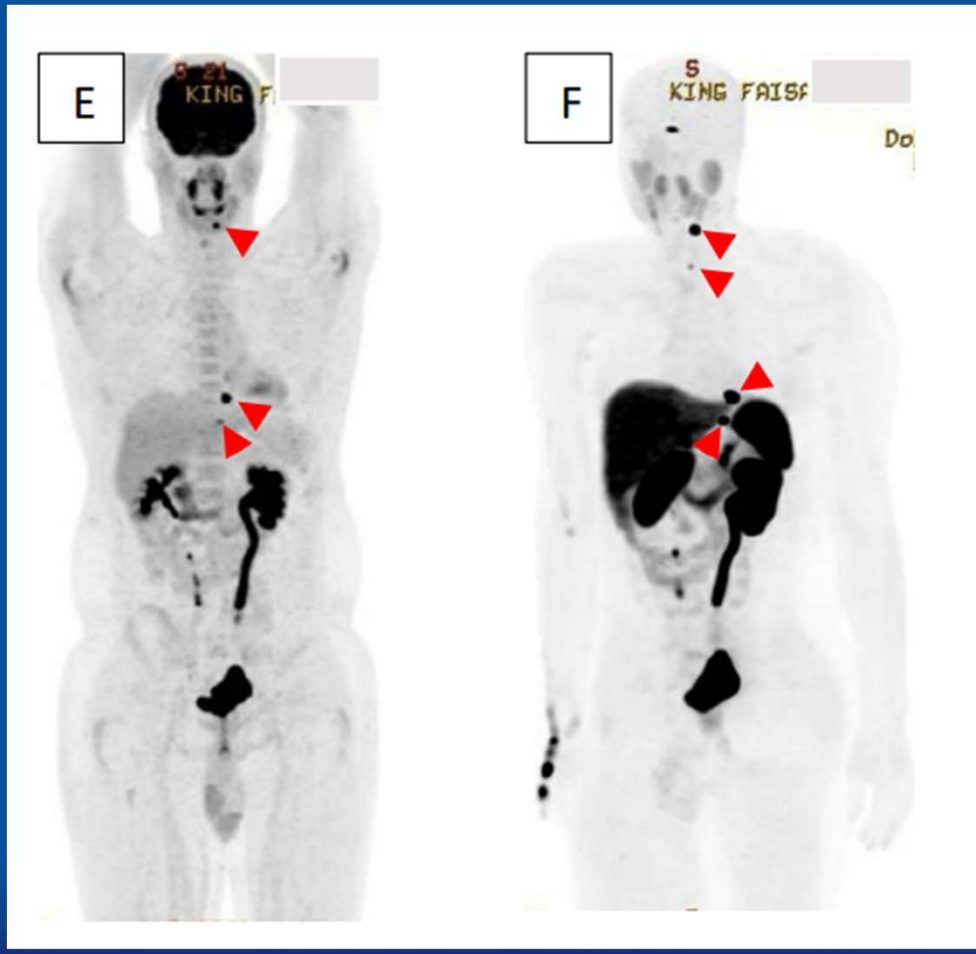






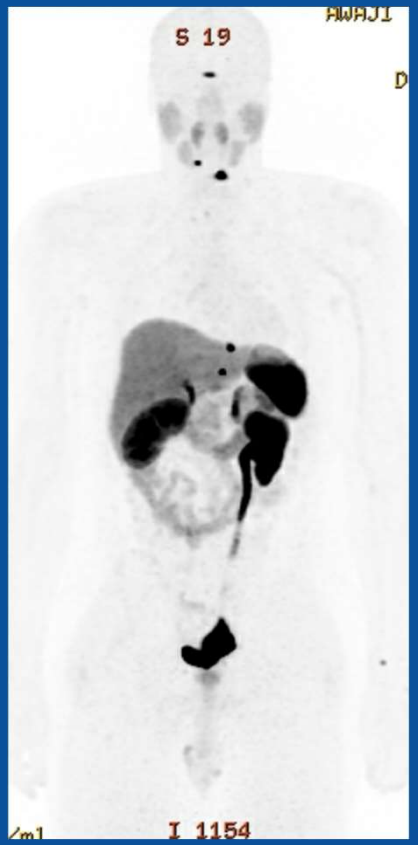


- Biopsy of thyroid nodule: pap. Thyroid cancer
- Underwent surgical resection of PGL IN February 2020
- 11 cm PGL locally invasive with vascular invasion, Ki67 40%
- August 2020: total thyroidectomy
- Pathology: tall cell variant PTC, bilateral, multifocal, largest 1.5 cm
- 11/16 Lymph nodes positive for mets
- Received I131 therapy for PTC

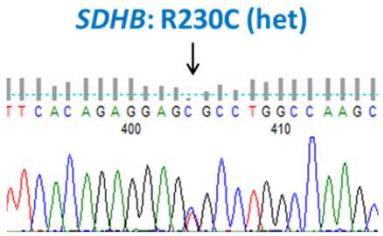


8/2023

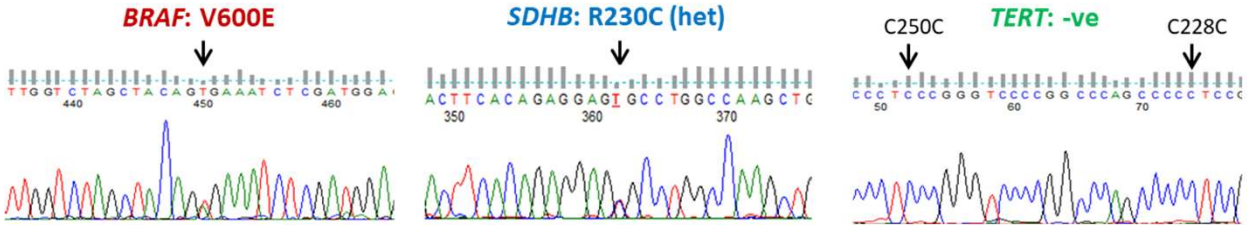
- Received 6 doses of Lu177 between March-October 2022
- External radiotherapy 5 sessions left 9th rib area
- Stable for the last 14 months



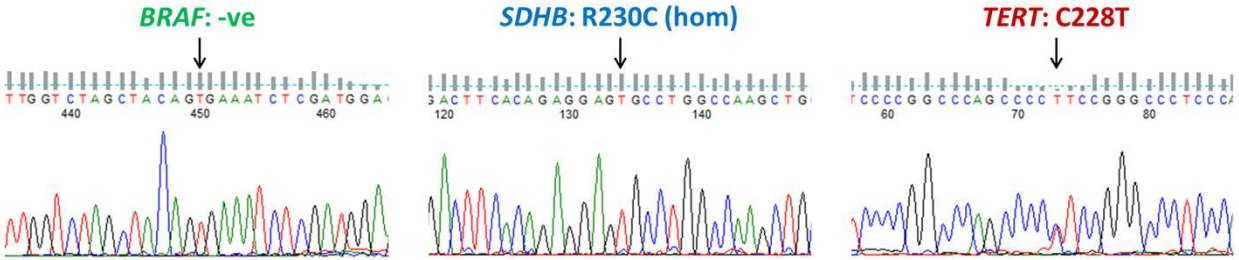
(A) Germline



(B) Papillary Thyroid Cancer



(C) Paraganglioma



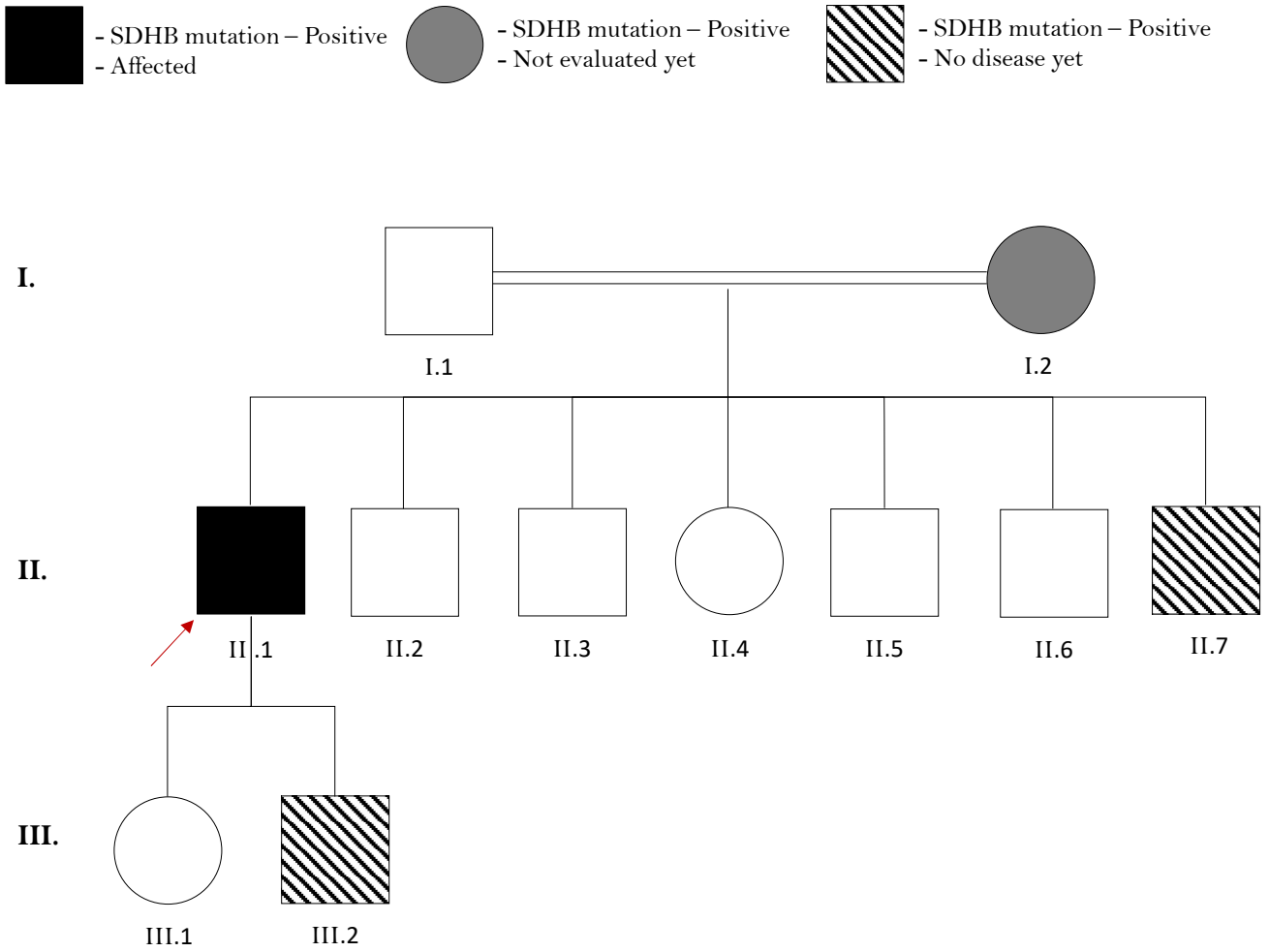

- SDHB mutation – Positive
- Affected
- SDHB mutation – Positive
- Not evaluated yet
- SDHB mutation – Positive
- No disease yet
I.
II.
III.
I.1
I.2
II.1
II.2
II.3
II.4
II.5
II.6
II.7
III.1
III.2

Figure 2

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

Follow-up of cluster 1 mutation carriers *with a history* of a PPGL	History of metastatic PPGL, history of sympathetic PGL, *SDHA/B, FH HIF2A/EPAS1*-related PPGLs	History of head and neck PGL, *SDHC/D/AF2, VHL*
Biochemistry	6-12 months (for HIF2A/EPAS1 including hematocrit)	12 months
Imaging (MRI base of the skull to pelvis, possibly alternating with low-dose chest CT plus MRI base of the skull, neck, abdomen, pelvis)	12-24 months (initially 12, then 12-24 months)	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.

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

Nolting S, et al. Endocrine Reviews: 43:199–239, 2022

Ongoing studies	Therapy	Patient number (n)	Status
NCT04394858	PARP inhibitor olaparib plus temozolomide (phase II, prospective)		Recruiting
NCT01850888	[^{131}I]-MIBG		Recruiting
NCT00107289	[^{131}I]-MIBG (phase II, prospective)		Recruiting
NCT04029428	[^{177}Lu] DOTATATE vs [^{90}Y] DOTATATE vs mix each of 50% (PRRT) (phase II, prospective)		Recruiting
NCT03206060	[^{177}Lu] DOTATATE (Lutathera) (PRRT) (phase II, prospective)		Recruiting (SDHx-related and sporadic PPGLs)
NCT04276597	^{177}Lu] DOTATOC (PRRT) (phase II, prospective)		Recruiting
NCT04711135	[^{177}Lu] DOTATATE (Lutathera) (PRRT) in adolescents (phase II, prospective)		Not yet recruiting
NCT03923257	[^{177}Lu] DOTATATE (PRRT) in children and adolescents (phase I/II, prospective)		Recruiting
LAMPARA NCT03946527	Lanreotide (cold somatostatin analog) (phase II, prospective)		Not yet recruiting
NCT03034200	Dopamine receptor D2 and caseinolytic protease P (ClpP) agonist ONC201(phase II, prospective)		Recruiting
NCT04284774	Farnesyltransferase inhibitor tipifarnib (RAS inactivation) (phase II, prospective)		Recruiting
FIRST-MAPP Study, NCT01371201	TKI sunitinib (phase II, prospective, first randomized placebo-controlled study)	N = 74 (closed)	Data arriving soon
NCT03839498	TKI Axitinib (AG-013736) (phase II, prospective)		Recruiting
NCT03008369	TKI lenvatinib (phase II, prospective)		Active, not recruiting
NCT02302833	TKI cabozantinib (phase II, prospective)	N = 10	Recruiting (preliminary data from n = 10, partial response 40%, PFS 11.2)
NCT04400474	Cabozantinib plus atezolizumab (CABATEN) (phase II, prospective)		Recruiting
NCT02834013	Nivolumab plus ipilimumab (phase II, prospective)		Recruiting
NCT02721732	Pembrolizumab (phase II, prospective)		Recruiting
NCT02923466	VSV-IFNβ-NIS and avelumab(phase II, prospective)		Recruiting
NCT04187404	Novel Therapeutic Vaccine (EO2401) (phase I/II, prospective)		Recruiting

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