Clinical and molecular genetics of Carney Triad and the dyad of GIST and PGL/PHEOS (Carney-Stratakis syndrome)

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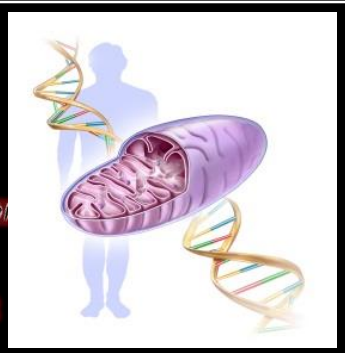
National Institute of Child Health & Human Development,
National Institutes of Health

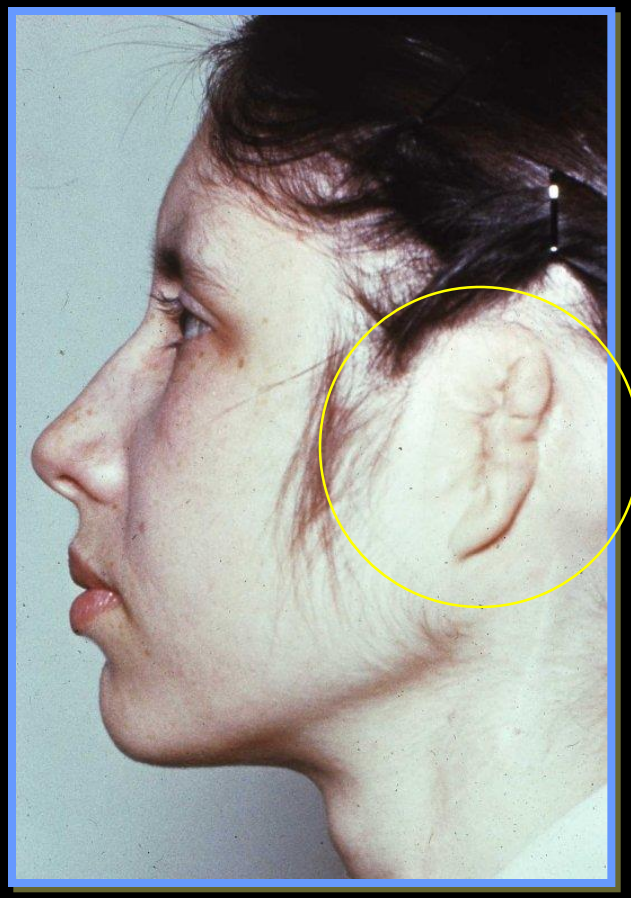
Pediatric and SDH-def GIST Symposium,
Miami, FL, July 14-15, 2018



SEGEN

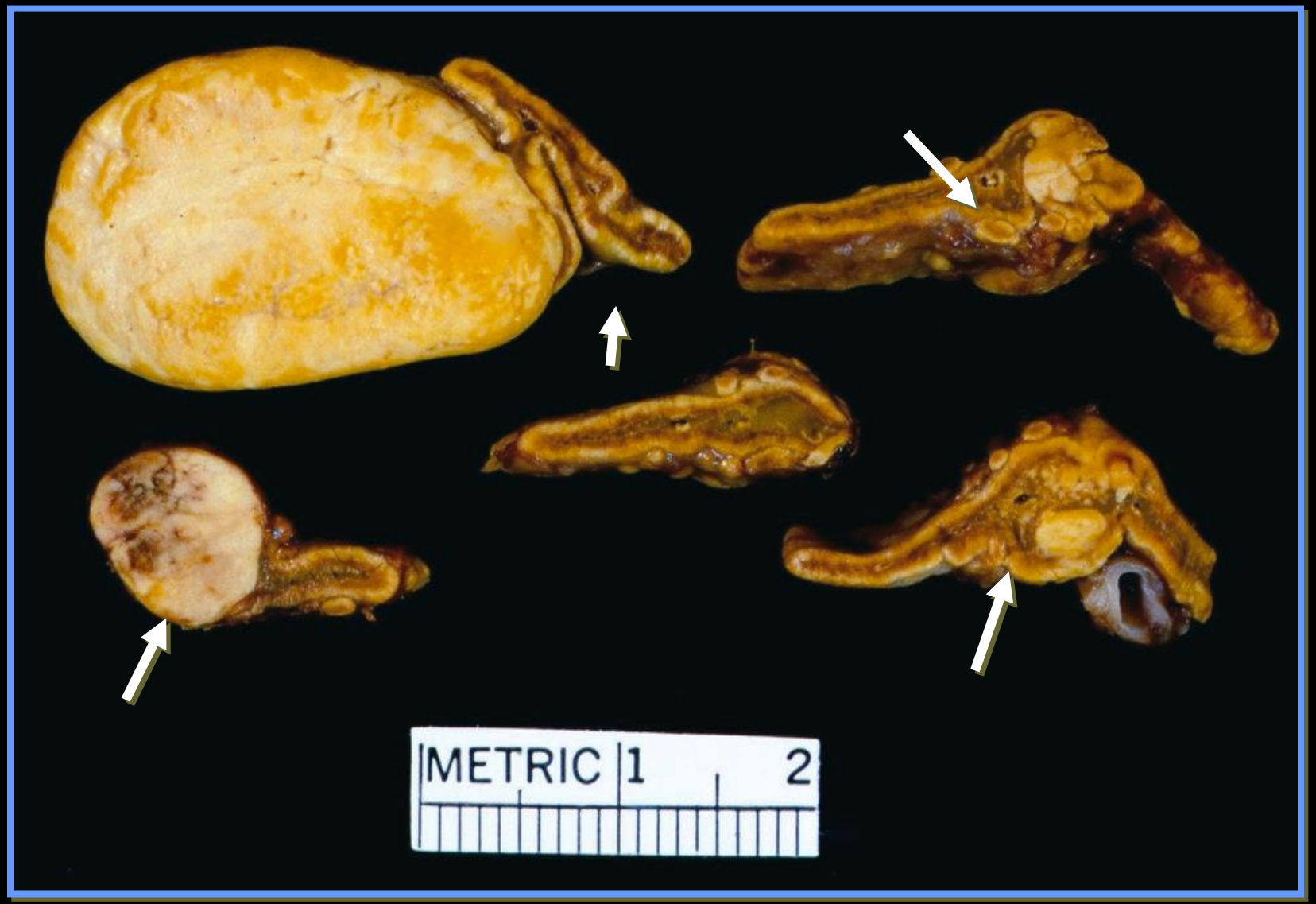
Carney Triad (OMIM #604287)

- Gastric stromal tumor (GIST)
- Pulmonary chondroma (PC)
- Paraganglioma (PGL)
- Pheochromocytoma (rarely)
- Adrenocortical adenoma & hyperplasia
- Hyperparathyroidism
- Thyroid tumors
- Pigmented lesions (lentigenes, nevi)
- Other hamartomatous lesions)

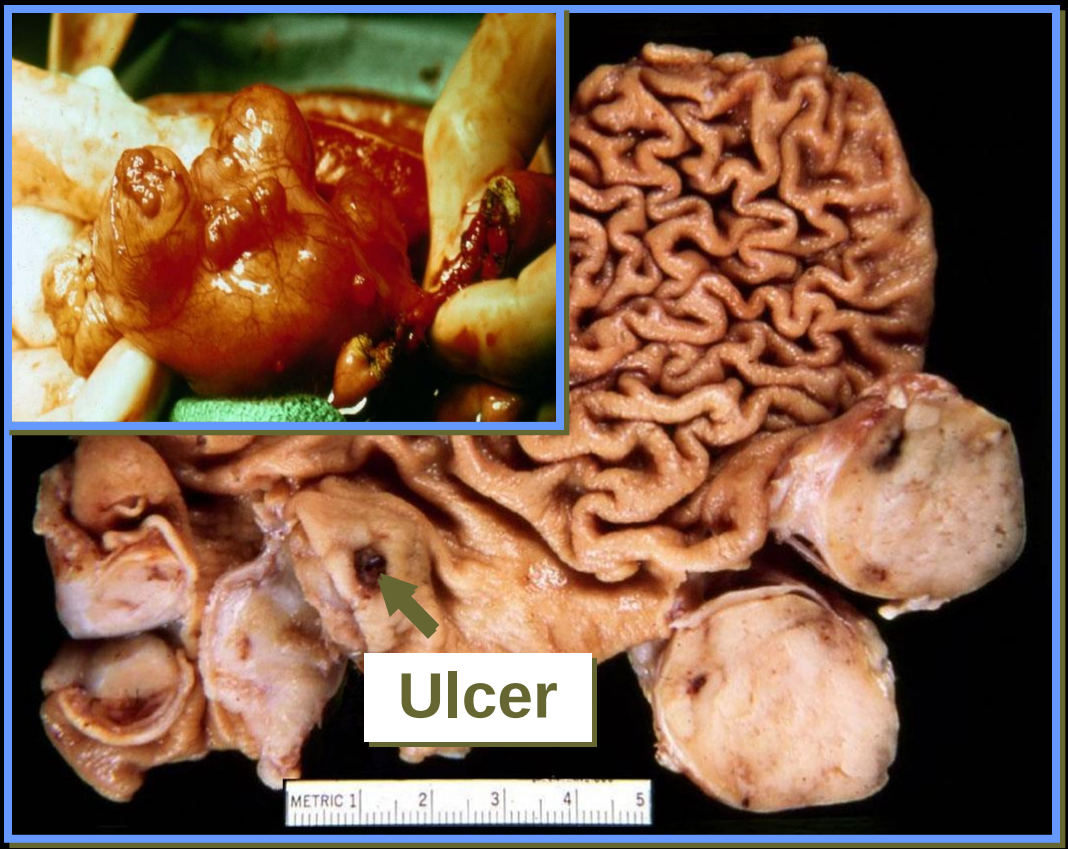


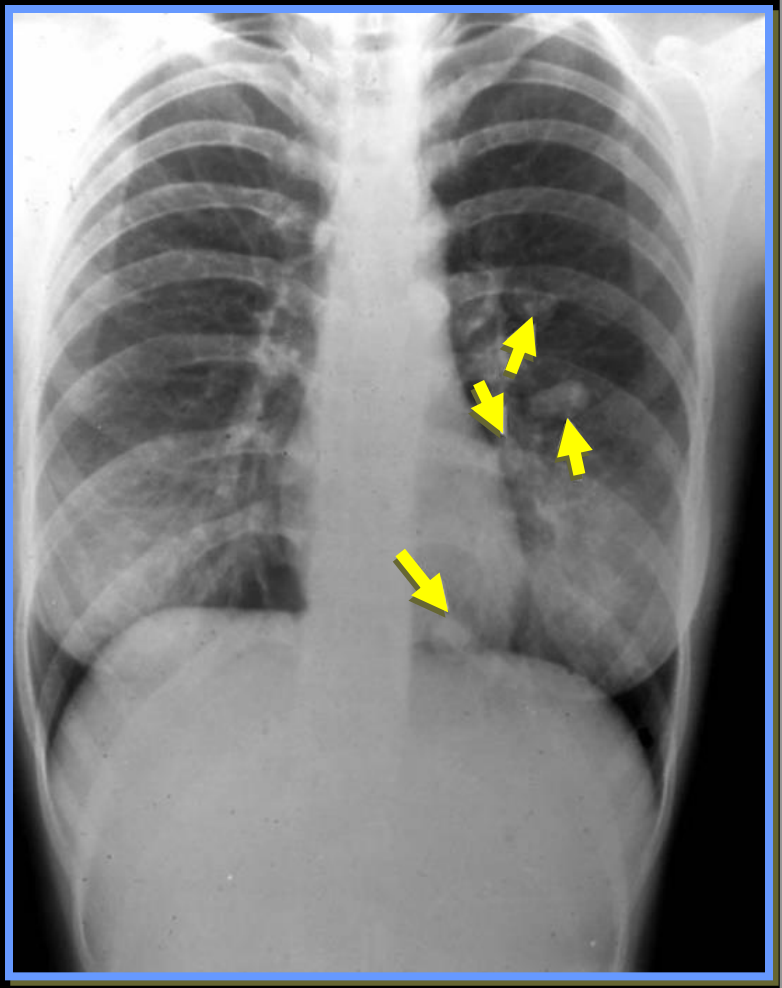
- *Carney JA, Sheps SG, Go VLW, Gordon H. N Engl. J. Med. 296;1517-18, 1977*
- *Carney JA. Mayo Clin Proc. 74:543-52, 1999*

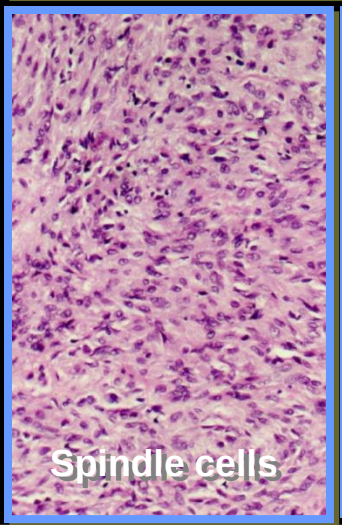
Genetic causes of adrenocortical tumors

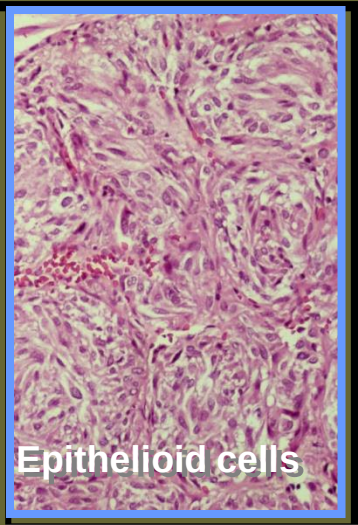


C. A. Stratakis NICHD, NIH

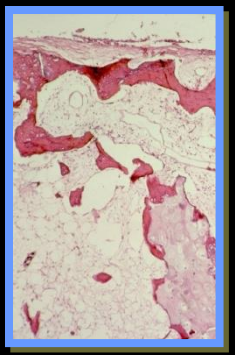








Gastro-Intestinal tumors



Pulmonary Chondroma

Am J Med (June 1981)

Aorticopulmonary Paraganglioma and Gastric Leiomyoblastoma in a Young Woman

MICHAEL P. GRACE, M.D.*
GERALD BATIST, M.D.†
WILLIAM R. GRACE, M.D.
JOHN F. GILLOOLEY, M.D.
New York, New York

The 16th report of a patient with "Carney's triad" is presented. The triad consists of an extra-adrenal paraganglioma, gastric leiomyoblastomas and a pulmonary chondroma. The diagnosis is made by discovery of the presence of at least two of these individually rare tumors. The patient described is a 15 year old girl who presented with a pericardial effusion caused by an invasive mediastinal paraganglioma. She was subsequently found to have multiple gastric leiomyoblastomas. The leiomyoblastomas have been resected. The paraganglioma was unresectable, and the patient underwent sequential radiation therapy and chemotherapy without response. Concomitant 5-fluorouracil chemotherapy with radiation resulted in an objective regression of the tumor mass.

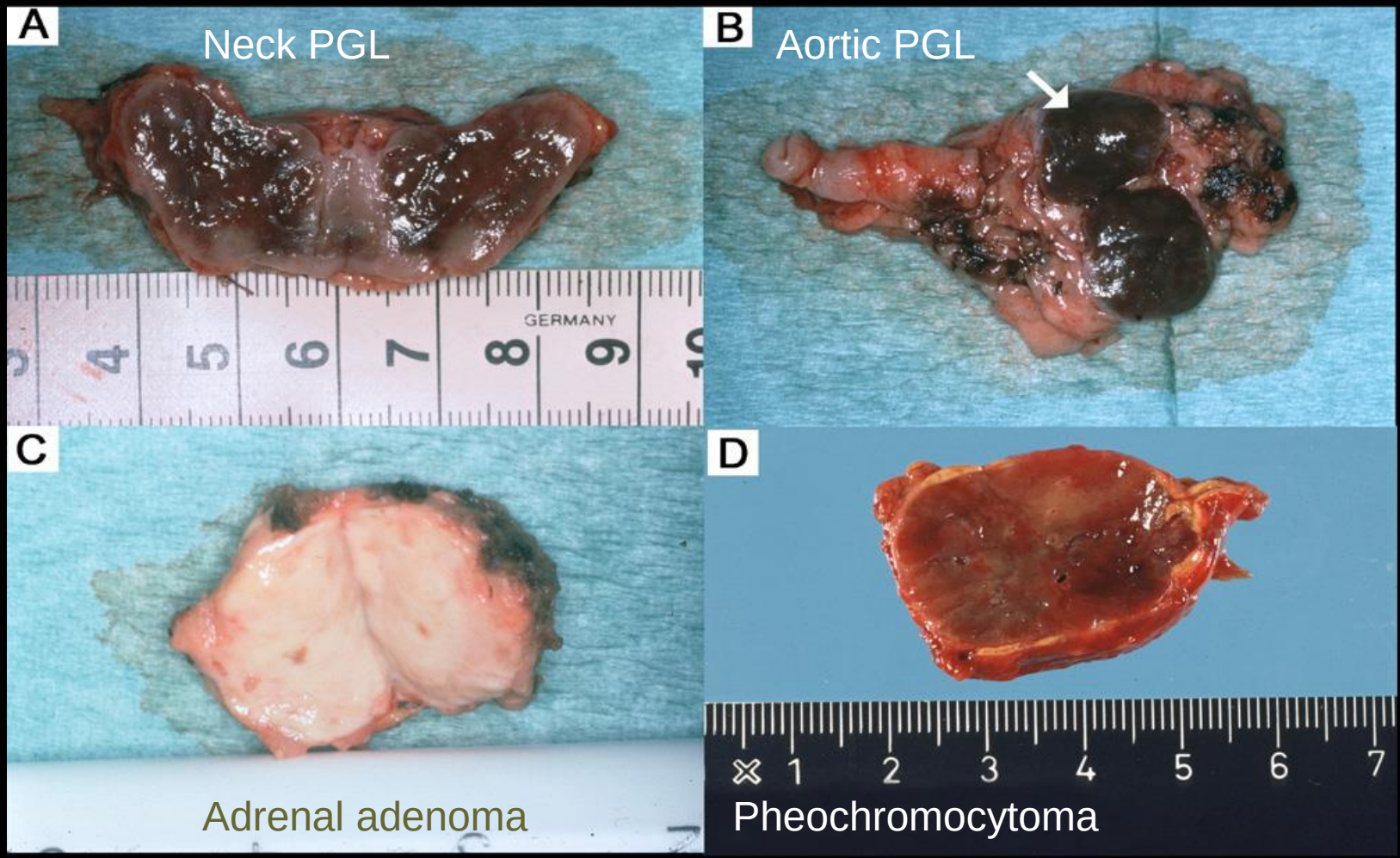
Carney Triad (OMIM #604287)

- 79 non-familial cases
- 67 females
- 12 males

- 78% of patients had two tumors
- 22% had three tumors at presentation

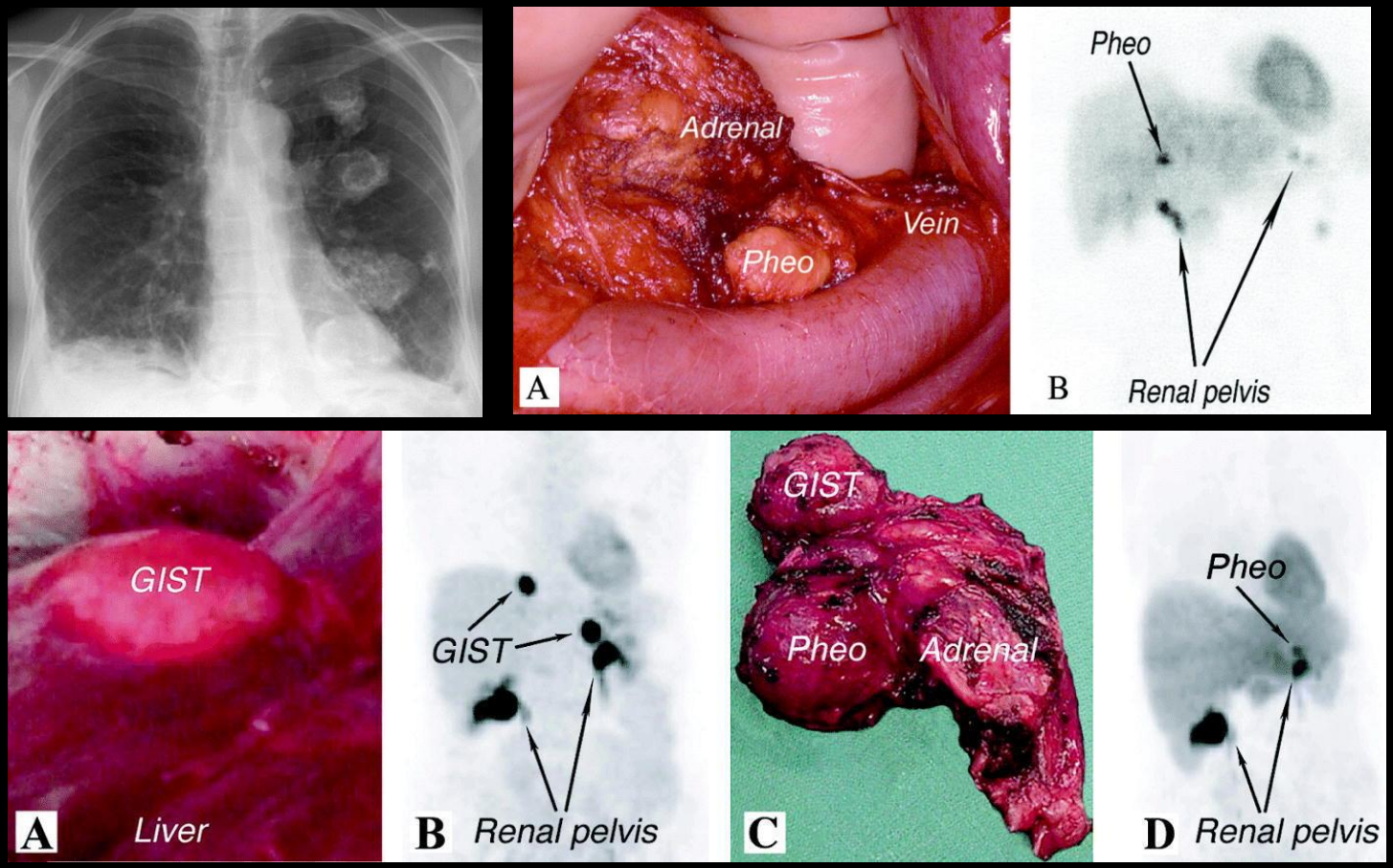
- 53% of patients had gastric and pulmonary tumors; 13% had (mostly nonfunctioning) adrenal tumors; other lesions were present

Carney, J. A. Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney triad): natural history, adrenocortical component, and possible familial occurrence. *Mayo Clin. Proc.* 74: 543-552, 1999.



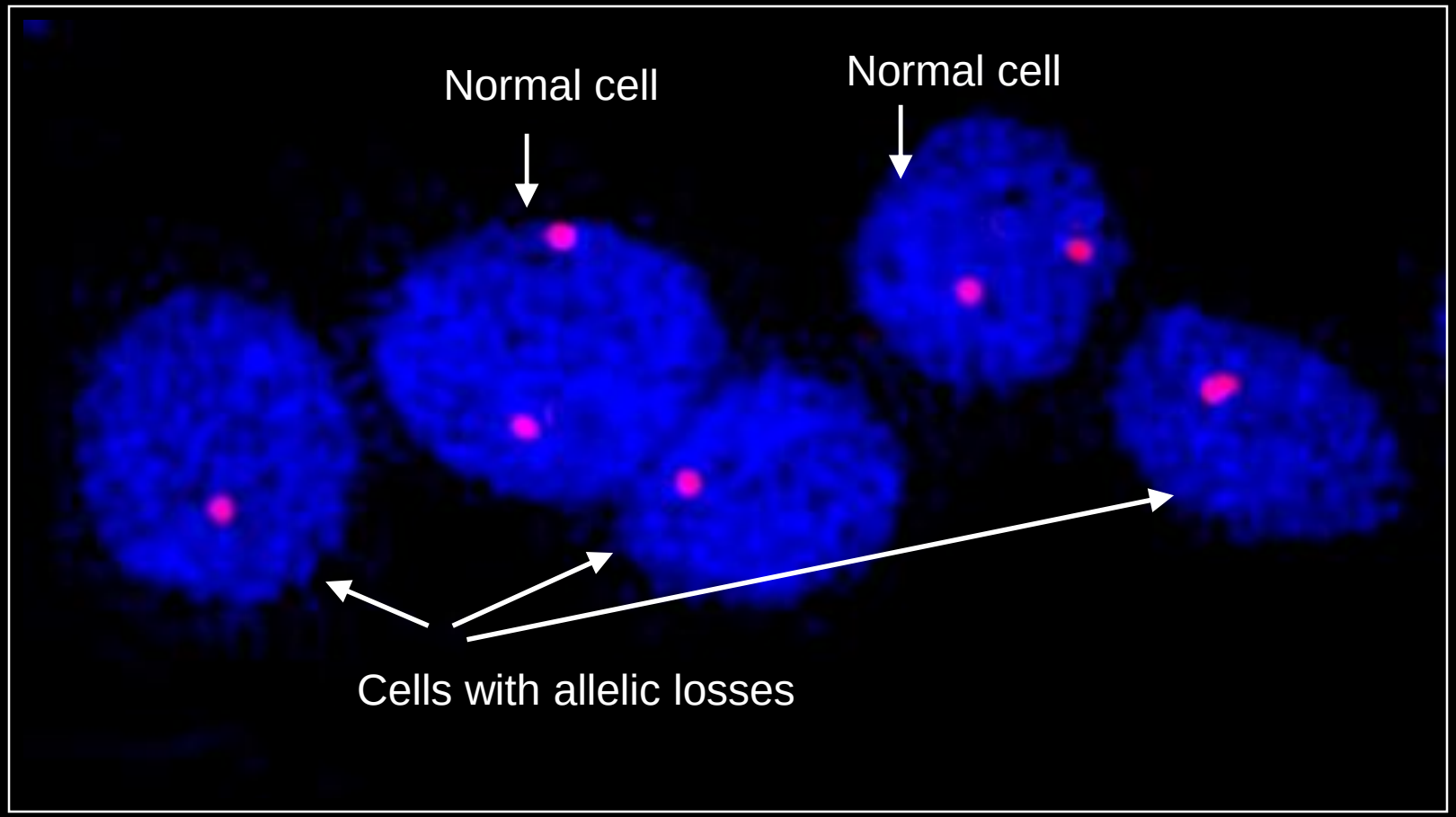
C. A. Stratakis NICHD, NIH

BUMMING et al. Scand. J. Gastroenterol., 2006; 41: 626-630



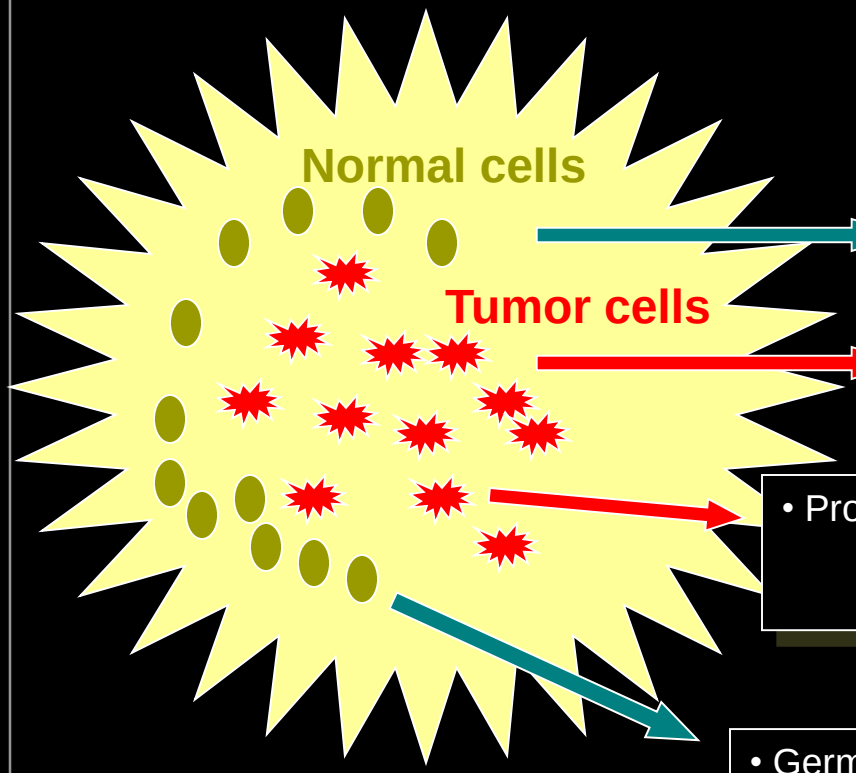
Although most patients present at a young age, late presentation is not unusual

Tumor specimens: the problem of admixture with normal cells:



Genetic causes of GIST

SOMATICs: The only program that can read both germline & somatic genetic information in a single heterogeneous tumor tissue sample

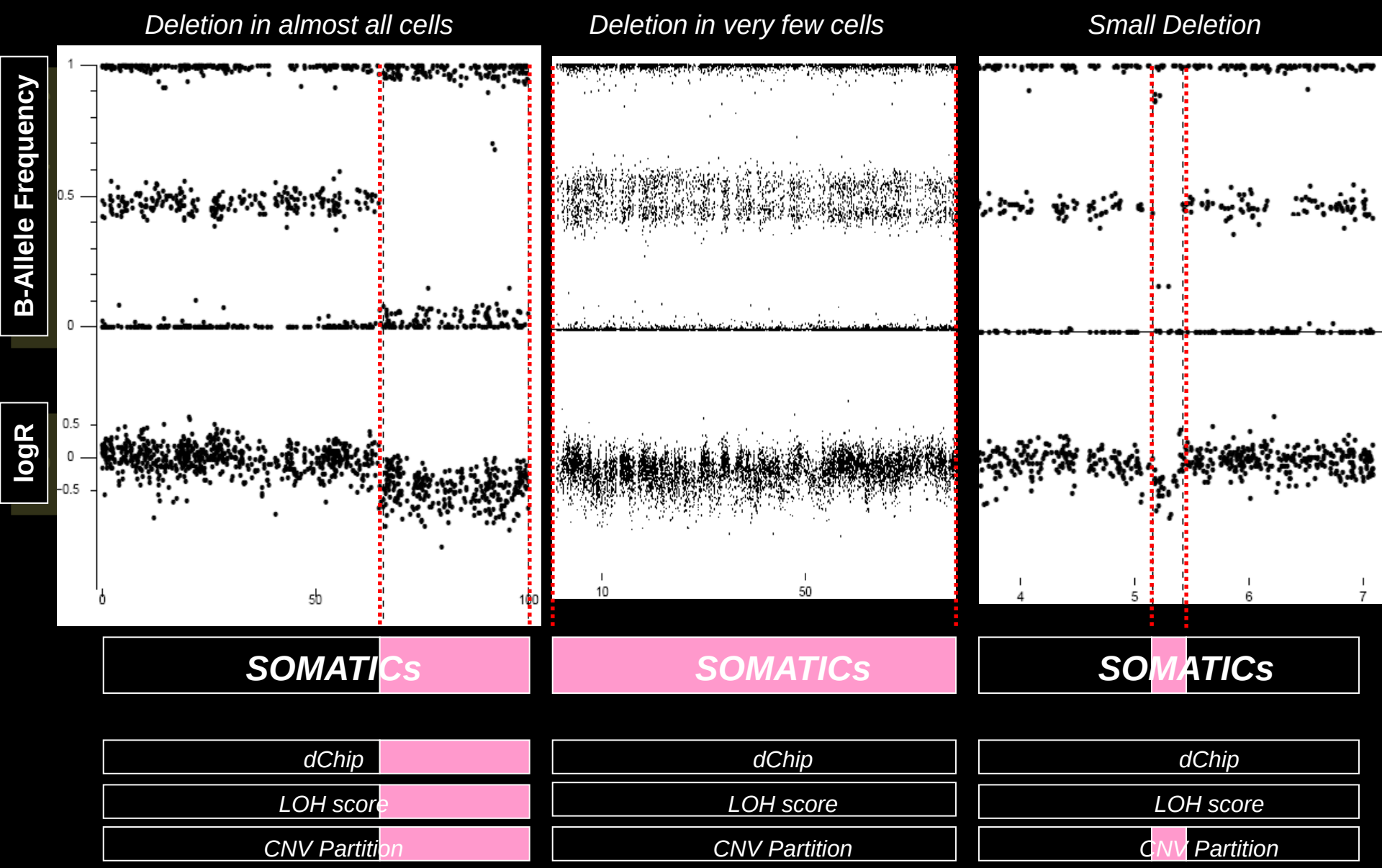


- Detection of deletions and amplifications
  - Automated
  - Sensitive
  - Discrimination somatic/germline

- Proportion of cells with a somatic deletion or amplification:
  - -Proportion of tumor cells in a tissue sample
  - -Discrimination early/late somatic events

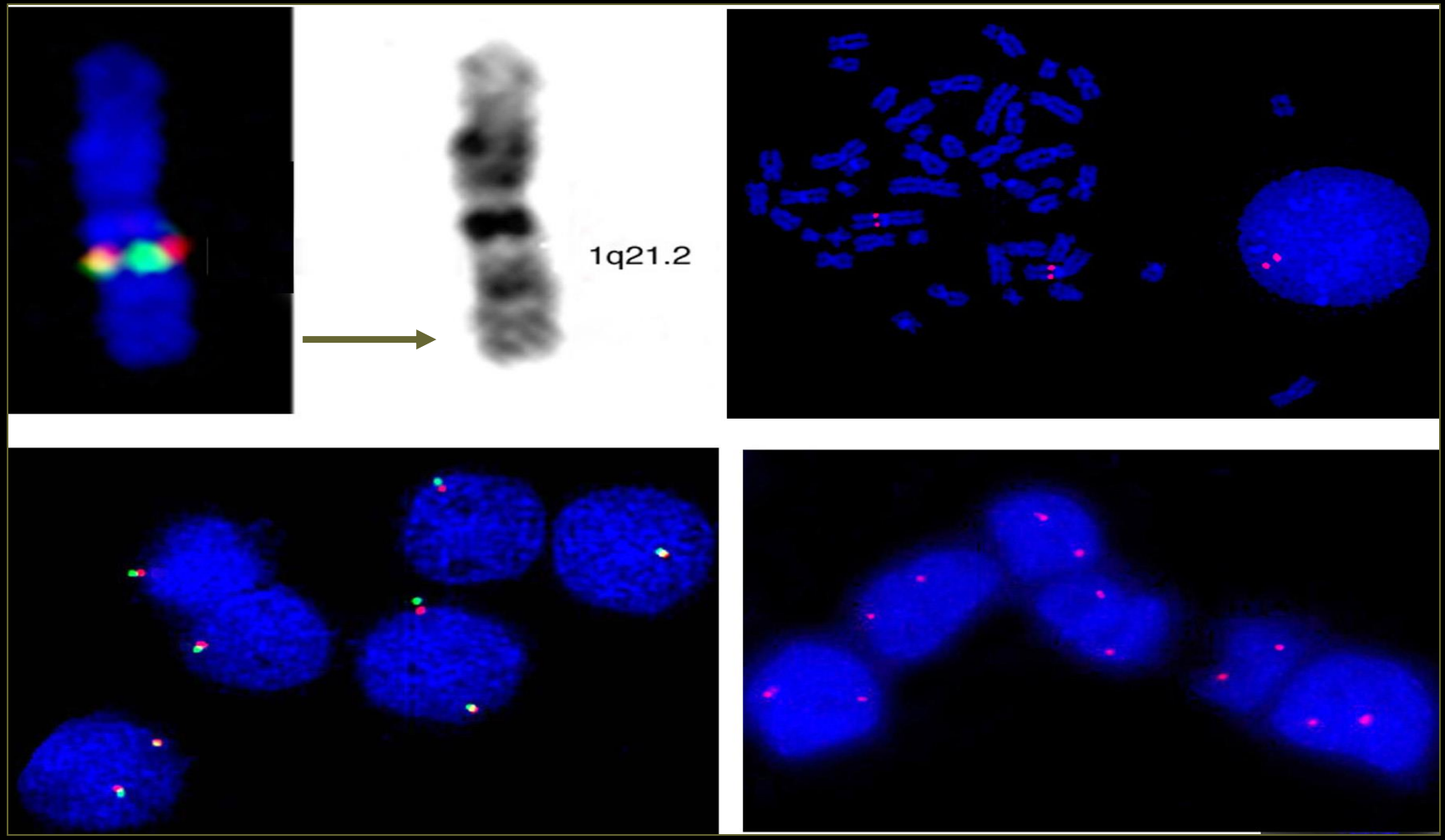
- Germline genotype

Sensitive & automatic detection of somatic deletions



Assié G, et al. Am J Hum Genet. 2008;82:903-15.

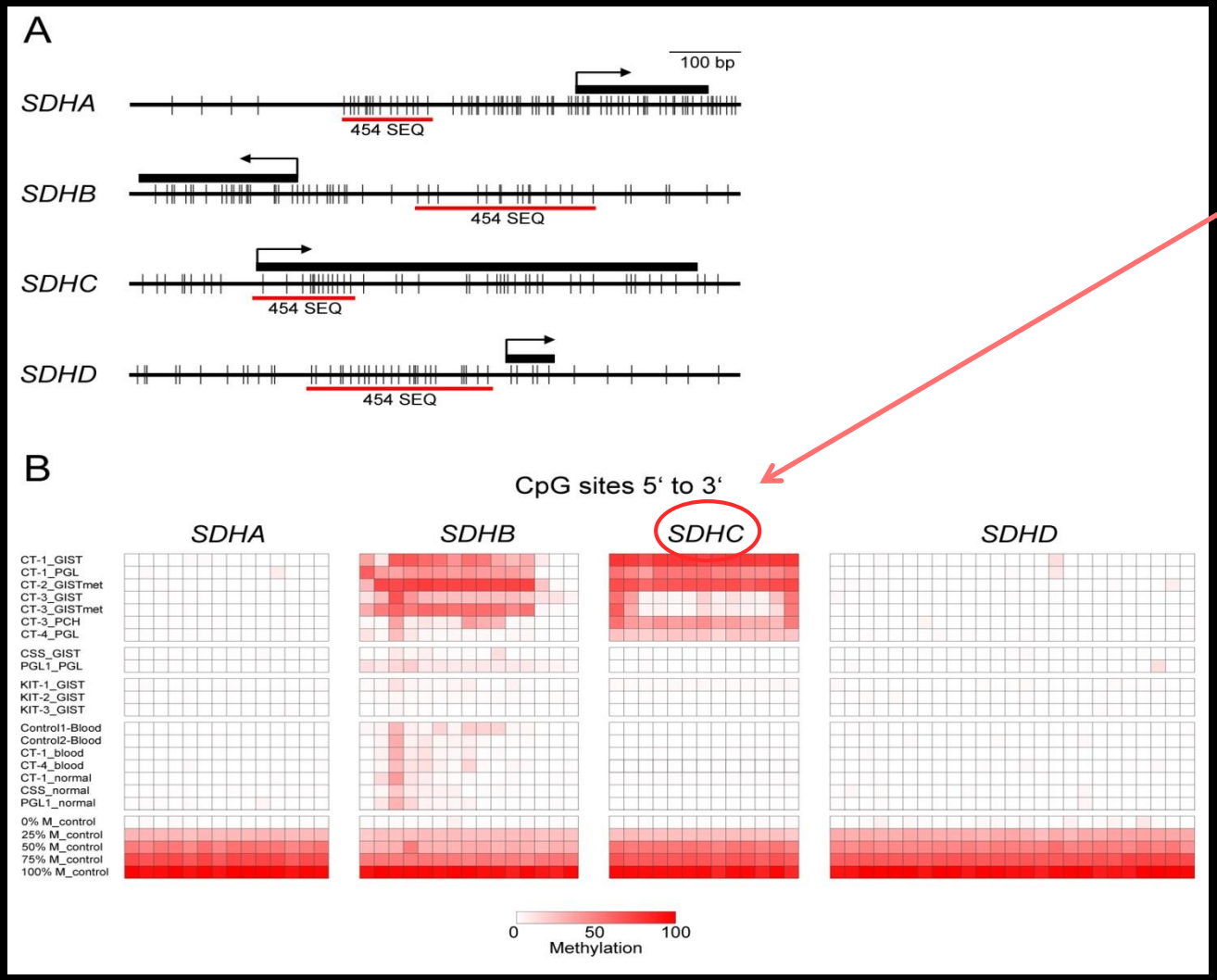
Carney Triad: CGH studies pointed to Chrom 1



Matyakhina et al. **Genetics of Carney triad: recurrent losses at chromosome 1, but lack of germline mutations in genes associated with paragangliomas and gastrointestinal stromal tumors. *J. Clin. Endocrinol. Metab*. 2007;92:2938-43**

Aberrant DNA hypermethylation of SDHC: A novel mechanism of tumor development in Carney Triad

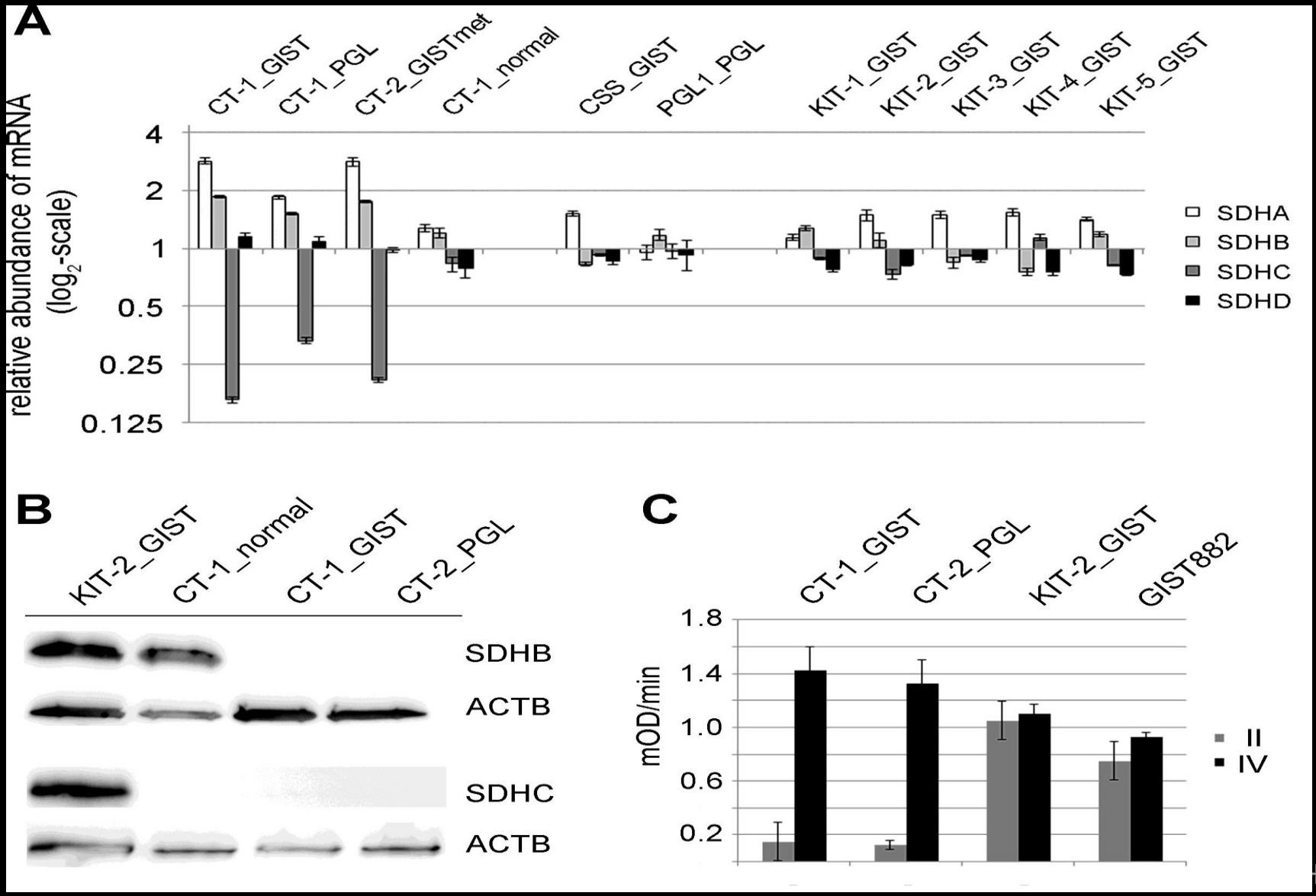
Haller F, *et al*. *Endocr Relat Cancer. 21(4):567-77, 2014*



SDHC-specific Methylation in Carney Triad

Aberrant DNA hypermethylation of SDHC: A novel mechanism of tumor development in Carney Triad

Haller F, *et al*. *Endocr Relat Cancer. 21(4):567-77, 2014*



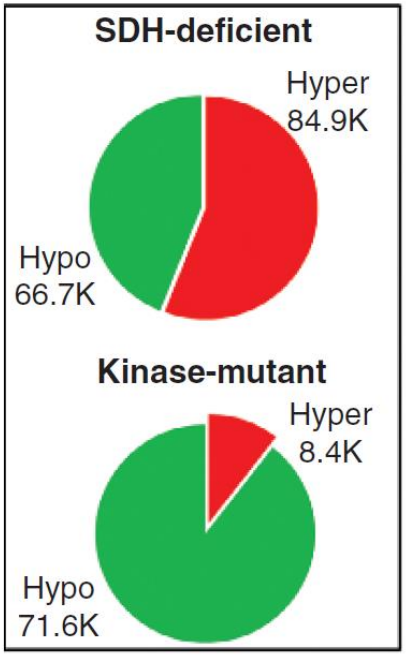
SDH Mutations Establish a Hypermethylator Phenotype in Paraganglioma

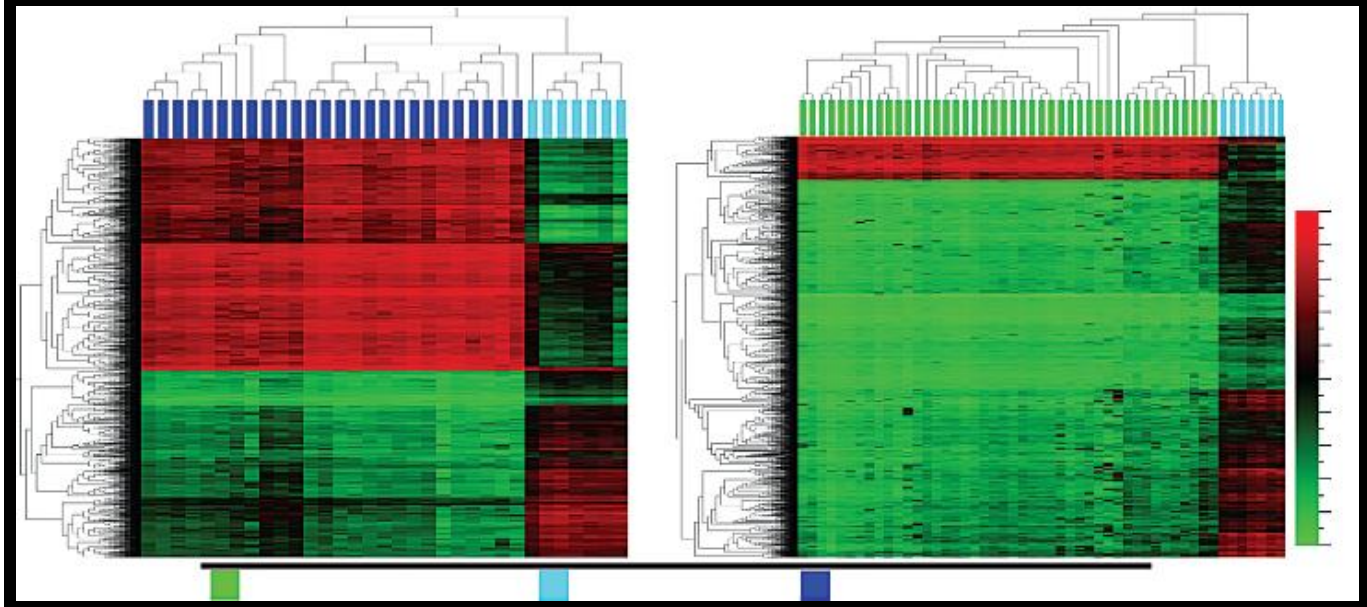
Cancer Cell 23, 739–752, June 10, 2013

Eric Letouzé,[1,13] Cosimo Martinelli,[2,3,13] Céline Loriot,[2,3] Nelly Burnichon,[2,3,4] Nasséra Abermil,[3,4] Chris Ottolenghi,[3,6,7] Maxime Janin,[6,7] Mélanie Menara,[2,3] An Thach Nguyen,[2,3] Paule Benit,[8] Alexandre Buffet,[2,3] Charles Marcaillou,[9] Jérôme Bertherat,[3,10,11,12] Laurence Amar,[3,5,12] Pierre Rustin,[8] Aurélien De Reyniès,[1] Anne-Paule Gimenez-Roqueplo,[2,3,4,12,14] and Judith Favier[2,3,14,*]

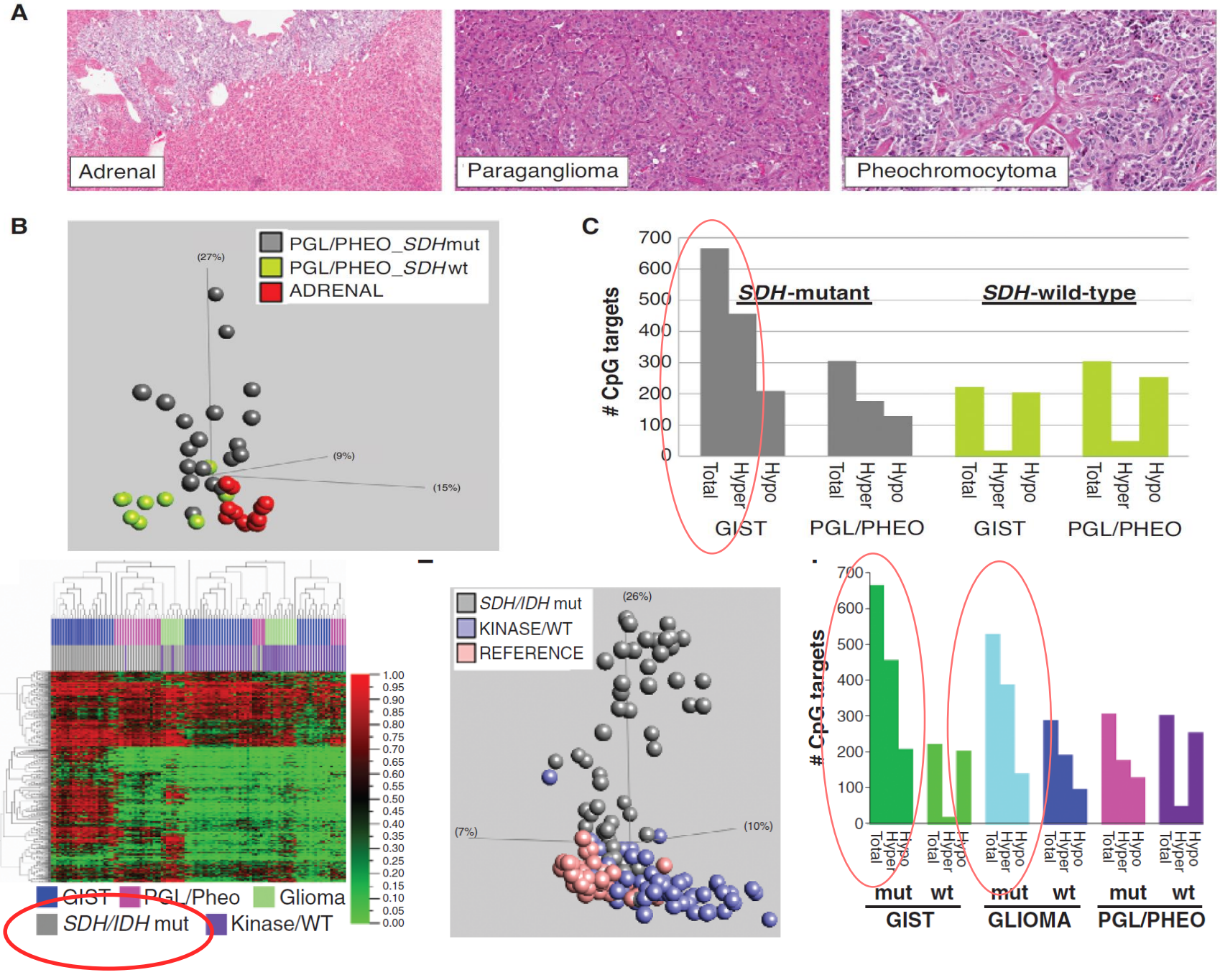
Succinate Dehydrogenase Mutation Underlies Global Epigenomic Divergence in Gastrointestinal Stromal Tumor

Killian K *et al*. Cancer Discov 3; 648-657, 2013





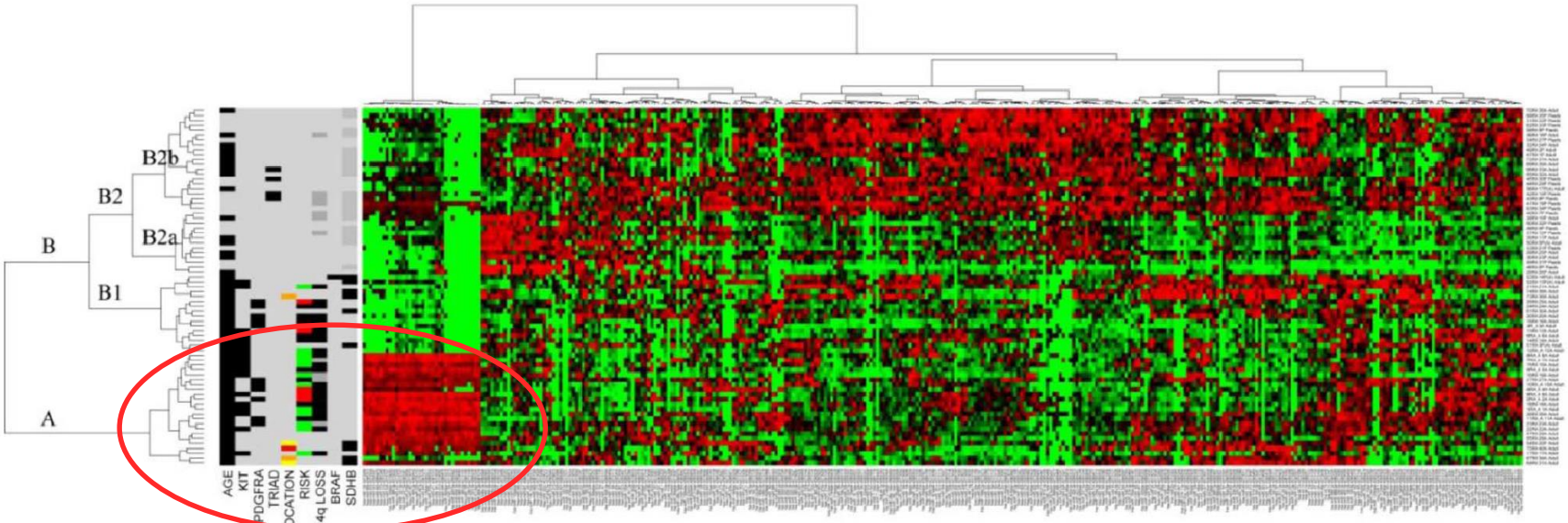
C. A. Stratakis NICHD, NIH


A
Adrenal
Paraganglioma
Pheochromocytoma
B
PGL/PHEO_SDHmut
PGL/PHEO_SDHwt
ADRENAL
(27%)
(9%)
(15%)
C
CpG targets
SDH-mutant
SDH-wild-type
Total
Hyper
Hypo
GIST
PGL/PHEO
GIST
PGL/PHEO
GIST
PGL/Pheo
Glioma
SDH/IDH mut
Kinase/WT
SDH/IDH mut
KINASE/WT
REFERENCE
(26%)
(7%)
(10%)
CpG targets
mut
wt
GIST
GLIOMA
PGL/PHEO

Post-Transcriptional Dysregulation by miRNAs Is Implicated in the Pathogenesis of Gastrointestinal Stromal Tumor [GIST]

PLOS ONE May 2013 | Volume 8 | Issue 5 | e64102

Lorna Kelly[1,2], Kenneth Bryan[3], Su Young Kim[4], Katherine A. Janeway[5], J. Keith Killian[4], Hans-Ulrich Schildhaus[6], Markku Miettinen[4], Lee Helman[4], Paul S. Meltzer[4], Matt van de Rijn[7], Maria Debiec-Rychter[8], Maureen O'Sullivan[1,2]*, NIH Pediatric and wild-type GIST Clinic[¶]



Strikingly different miRNA profiling for Carney Triad tumors

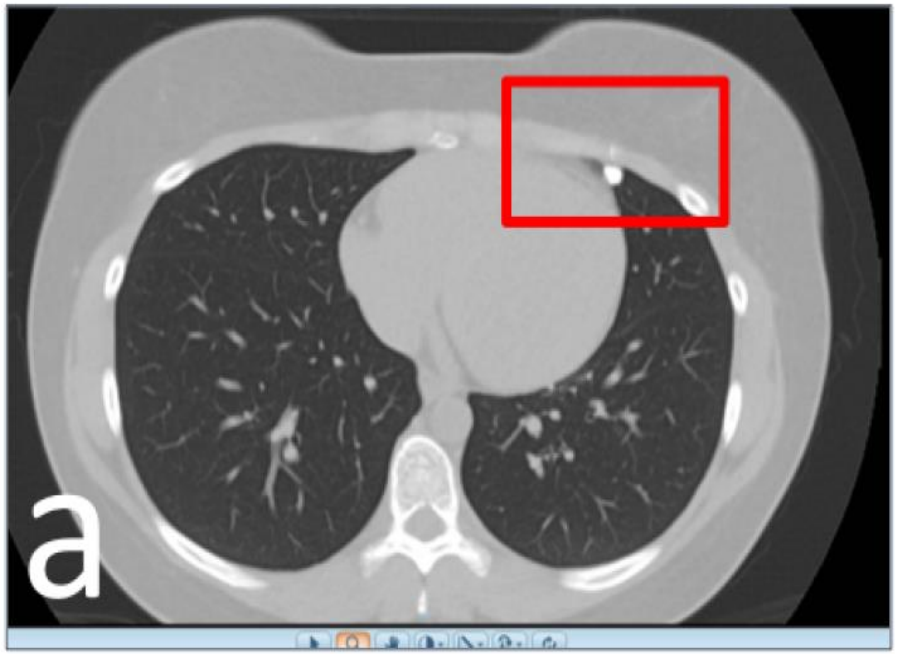
European Journal of Human Genetics (2016) 24, 569–573

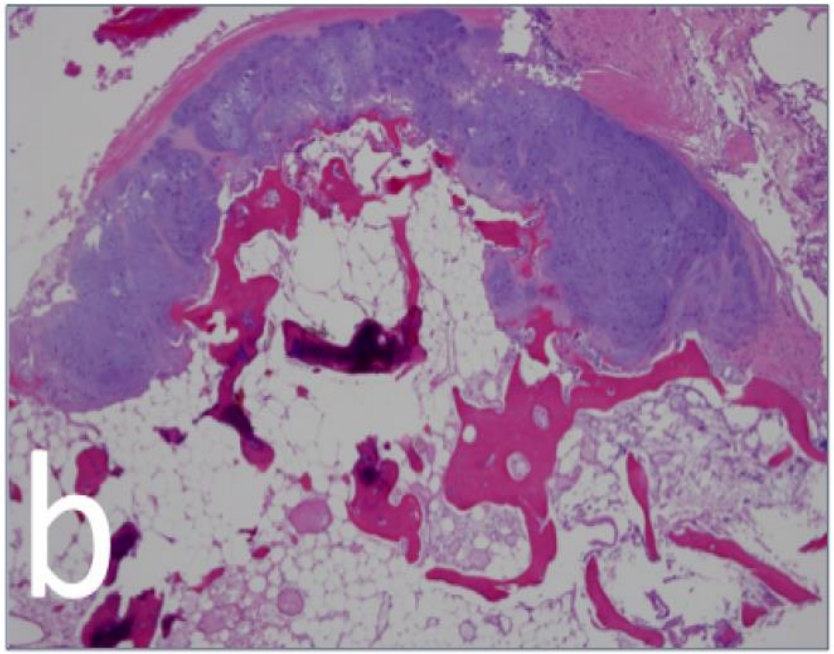
www.nature.com/ejhg

ARTICLE

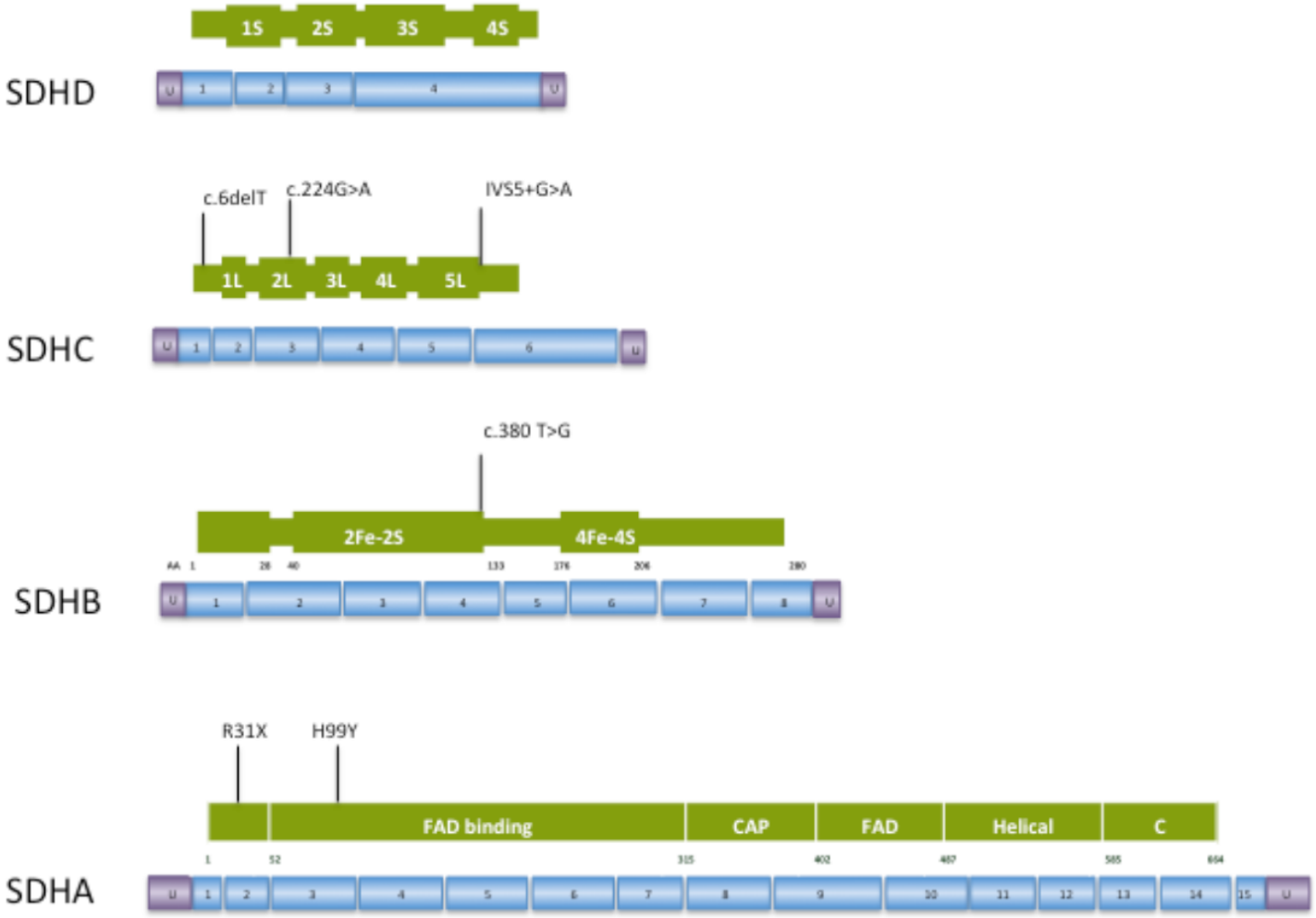
Carney triad can be (rarely) associated with germline succinate dehydrogenase defects

Sosipatros A Boikos[1,7,8], Paraskevi Xekouki[1,7], Elena Fumagalli[2], Fabio R Faucz[*,1], Margarita Raygada[1], Eva Szarek[1], Evan Ball[1], Su Young Kim[3], Markku Miettinen[4], Lee J Helman[3], J Aidan Carney[5], Karel Pacak[6] and Constantine A Stratakis[*,1]

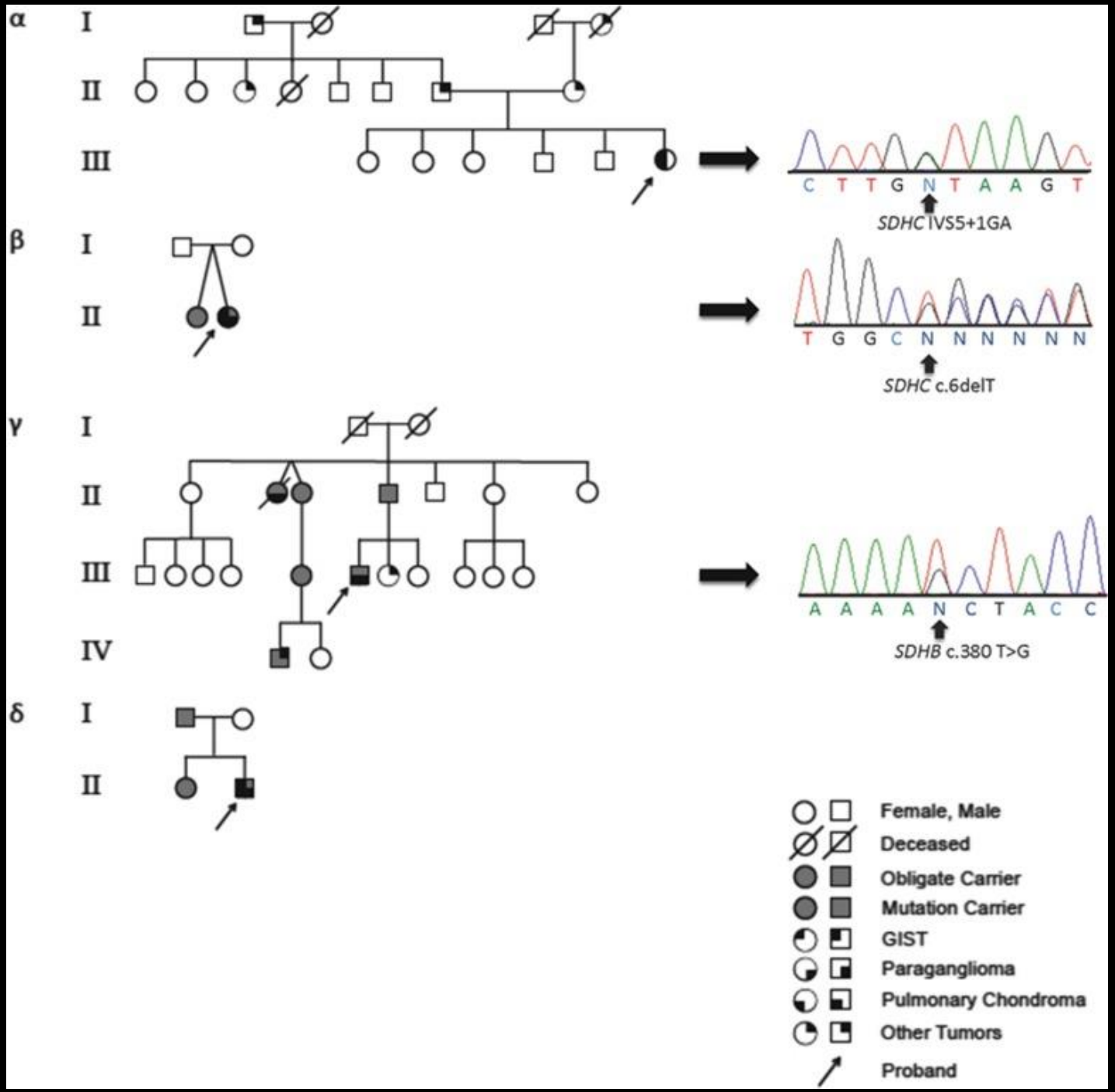




SDH Germline mutations in Carney Triad Patients



Eur J Hum Genet. 2016 Apr;24(4):569-73



Eur J Hum Genet.
2016
Apr;24(4):569-73

	Clinical Characteristics								Genetic Characteristics			
	Age at Diagnosis	Gender	GIST location	Paraganglioma	Chondroma	Other Tumors	Tumors in other family carriers	Carney Triad	Inheritance	Gene	Nucleotide	Type
CTR-NIH 12.03	13	Female	Stomach	No	Yes	No		Incomplete	No	SDHC	IVS5+G>A	Splice Type
CTR-NIH 602-03	20	Female	Stomach	No	Yes	Gaglioneuroma		Incomplete	No	SDHC	c.6delT	frameshift
CTR-NIH 593.01	28	Male	No GIST	Yes	Yes	No	Chondroma Paraganglioma Neuoblastoma	Incomplete	Yes	SDHB	c.380 T>G	Misence
CTR-NIH - ITA	20	Male	Stomach	Yes	Yes	No		Complete	No	SDHC	c.224G>A	Misense
CTR-NIH 808.01	11	Male	Stomach	No	Yes	No		Incomplete	No	SDHA	c.91 C>T	Stop Codon
CTR-NIH 72.02	21	Female	Stomach	No	Yes	No		Incomplete	No	SDHA	c.295>T	Misense

Patients were equally young when they presented (at the age of 21 years versus 23 years for the whole cohort), their tumors were not more or less aggressive, and they are all alive at the time of this publication. However, unlike the rest of the CTr patients who are overwhelmingly female, those with SDHx defects were disproportionately male (50% versus 8%, $P<0.05$) following the pattern of other diseases associated with SDHx mutations that typically have no gender predilection. The other interesting finding was the association with other neural crest tumors that have not previously been associated with CTr: ganglioneuroma in one patient with SDHC variation and NB in the nephew of another, in association with the same SDHB defect; in this family, no other patient had CTr: the obligate carriers had PGL or PHEO.

In other words, in accordance with all known CTr patients in whom the disease appears sporadically, even in these patients where SDHx mutations were present, CTr was never inherited in its full form.

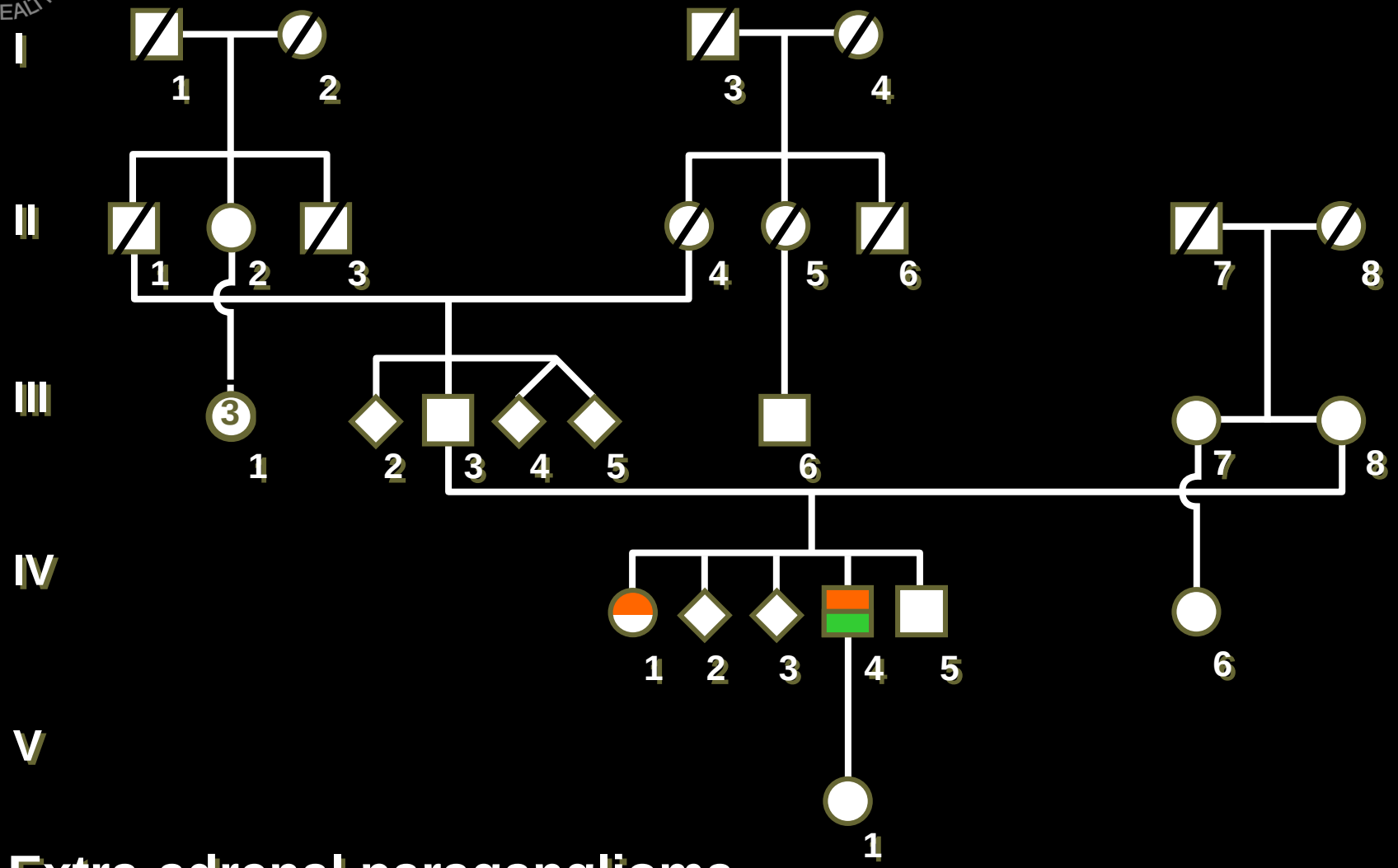
Eur J Hum Genet. 2016 Apr;24(4):569-73

Update on Carney Triad (July 2018):

- Genome-wide studies using multiple tumor samples have not revealed THE gene (yet!) – but:
- There is a small number (less than 10%) of Carney Triad patients with SDHx germline mutations
- Somatic deletions and methylation of chromosome 1 areas (SDHB, SDHC) are found in up to 1/3 of tumors associated with Carney Triad
- *SHDC*-specific methylation is present in all tumors studied to date but not in normal tissues from patients with the Triad
- There is widespread methylation of the genome in Carney Triad samples, as in other SDHB-deficient (at the protein level) tumors and in IDH mutations
- The miRNA profile of Carney Triad tumors is similar to that of other SDHB-deficient tumors

Genetic causes of GIST –PGL/PHEOs

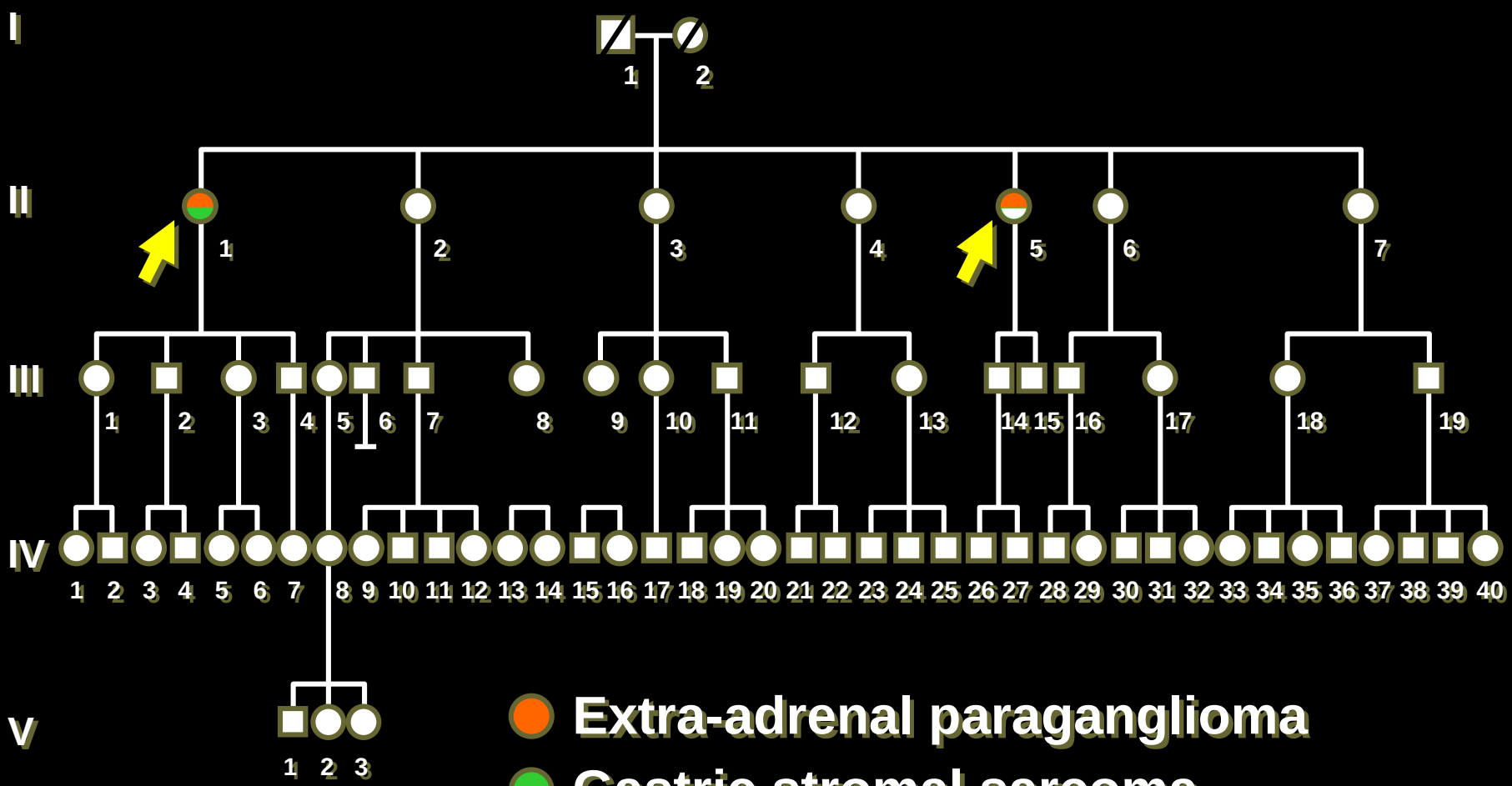
Family 1



- Extra-adrenal paraganglioma
- Gastric stromal sarcoma

C. A. Stratakis NICHD, NIH

Family 2



C. A. Stratakis NICHD, NIH

Monozygotic twins at age 5

LB alive with inoperable cervical paraganglioma and small adrenal nodule at age 55

American Journal of Medical Genetics 108:132–139 (2002)

Familial Paraganglioma and Gastric Stromal Sarcoma: A New Syndrome Distinct From the Carney Triad

J. Aidan Carney[1]* and Constantine A. Stratakis[2]

[1]*Department of Laboratory Medicine and Pathology (Emeritus member), Mayo Clinic and Foundation, Rochester, Minnesota*

[2]*Unit on Genetics and Endocrinology, Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland*

Paragangliomas may be inherited in an autosomal dominant manner either alone (as in PGL1, PGL2, and PGL3 syndromes) or as a component of a multiple tumor syndrome (as in von Hippel-Lindau disease and neurofibromatosis type 1). In this article, we describe 12 patients (7 male and 5 female) with an average age of 23 years from five unrelated families that manifested paraganglioma and gastric stromal sarcoma; the tumors were inherited in an apparent auto-

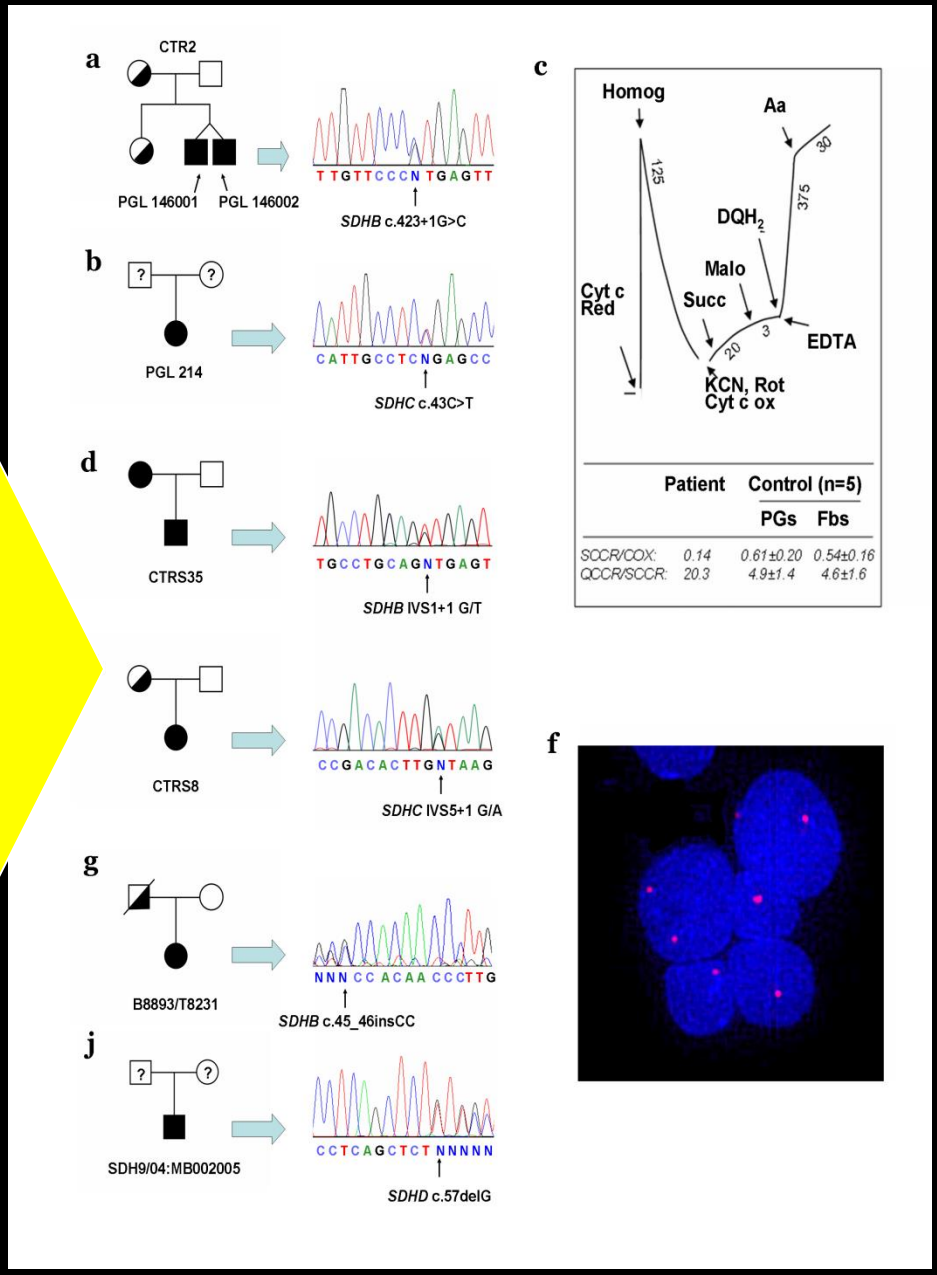
INTRODUCTION

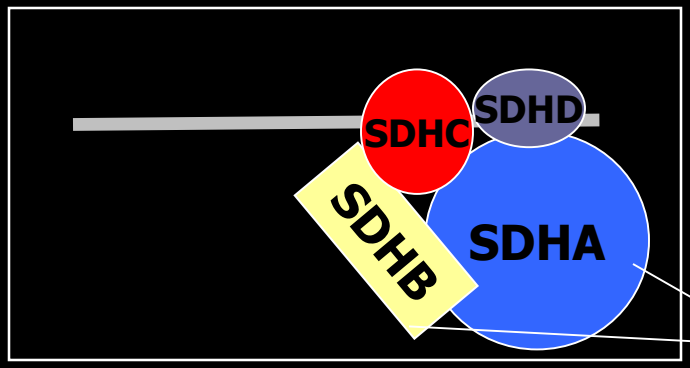
In 1977, Carney et al. [1977] reported the association of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma, and pulmonary chondroma in two patients and two of the three tumors in five other patients, all unrelated young females. The pattern and age of tumor occurrence—multifocal lesions in multiple organs in young patients—suggested a heritable disorder. The association was subsequently referred to as the Carney triad [Grace et al., 1981; OMIM, 2001, #604287].

Genetic causes of GIST

Patients with the *dyad of paragangliomas and gastric stromal sarcomas* have mutations In succinate dehydrogenase subunit genes (SDHB, -C, -D)

McWhinney SR, Pasini B & Stratakis CA. N Engl J Med. 2007;357:1054-6





Succinate dehydrogenase catalytic activity

the NIH Pediatric & Wildtype GIST Clinic

George Demetri	Medical Oncologist	Dana Farber Cancer Institute
Suzanne George	Medical Oncologist	Dana Farber Cancer Institute
Katherine Janeway	Pediatric Oncologist	Boston Children's Hospital
Michael La Quaglia	Pediatric Surgeon	Memorial Sloan Kettering
Alberto Pappo	Pediatric Oncologist	St Jude Children's Hospital
Joshua Schiffman	Pediatric Oncologist	Huntsman Cancer Institute
Jonathan Trent	Medical Oncologist	MD Anderson Cancer Center
Margaret von Mehren	Medical Oncologist	Fox Chase Cancer Center
Jennifer Wright	Pediatric Oncologist	Huntsman Cancer Institute
Lee Helman	Pediatric Oncologist	NCI
Su Young Kim	Pediatric Oncologist	NCI
Karel Pacak	Endocrinologist, NICHD	
Constantine Stratakis	Geneticist – Endo/gist	NICHD
Tricia McAleer	Life Raft Group	
Phyllis Gay	GIST Support International	

PNAS

Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking *KIT* and *PDGFRA* mutations

Katherine A. Janeway[a,1,2], Su Young Kim[b,1], Maya Lodish[c], Vânia Nosé[d], Pierre Rustin[e], José Gaal[f], Patricia L. M. Dahia[g], Bernadette Liegl[h], Evan R. Ball[c], Margarita Raygada[i], Angela H. Lai[a], Lorna Kelly[j], Jason L. Hornick[k], NIH Pediatric and Wild-Type GIST Clinic[l,m,n,o,p,3], Maureen O'Sullivan[j,q], Ronald R. de Krijger[f], Winand N. M. Dinjens[f], George D. Demetri[r], Cristina R. Antonescu[s], Jonathan A. Fletcher[k], Lee Helman[b], and Constantine A. Stratakis[c]

- *SDHB,-C,-D* mutations are present in ~12% if of patients with WT-GISTs with no personal or family history of PGL.

- SDHx mutations identify a category of GISTs with an oncogenic mechanism distinct from increasing c-KIT activity

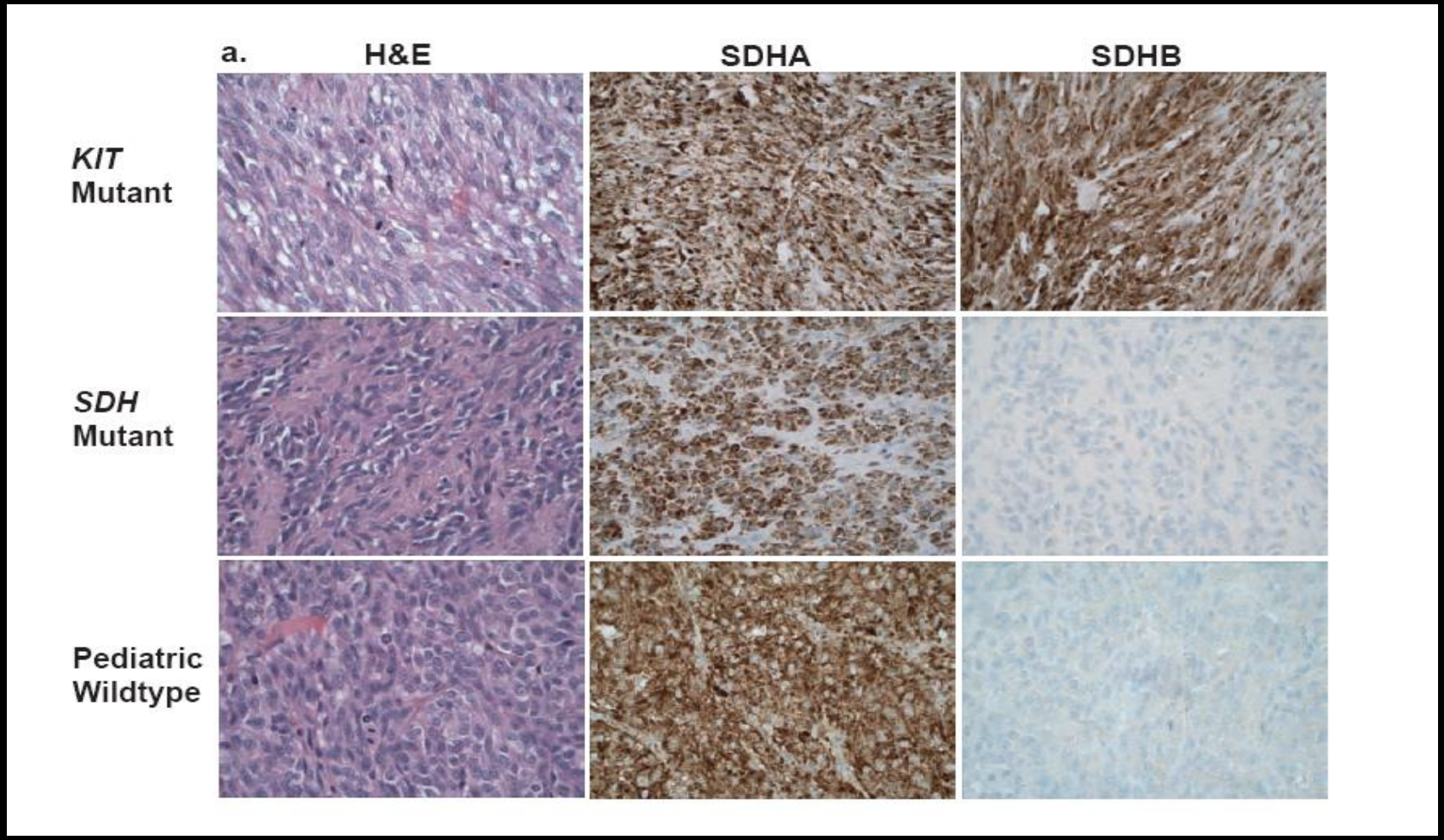
- SDHB immunohistochemistry and functional enzymatic assays show SDHx mutations lead to defects in mitochondrial oxidation and cell respiration

www.pediatricgist.cancer.gov/

Proc Natl Acad Sci U S A. 108(1):314-8, 2011.

SDHx Defects in GISTs: [Janeway et al. PNAS 2011] The NIH GIST clinic data (2008-2011)

Sporadic KIT and PDFGRA-negative GIST is almost always SDHB-negative

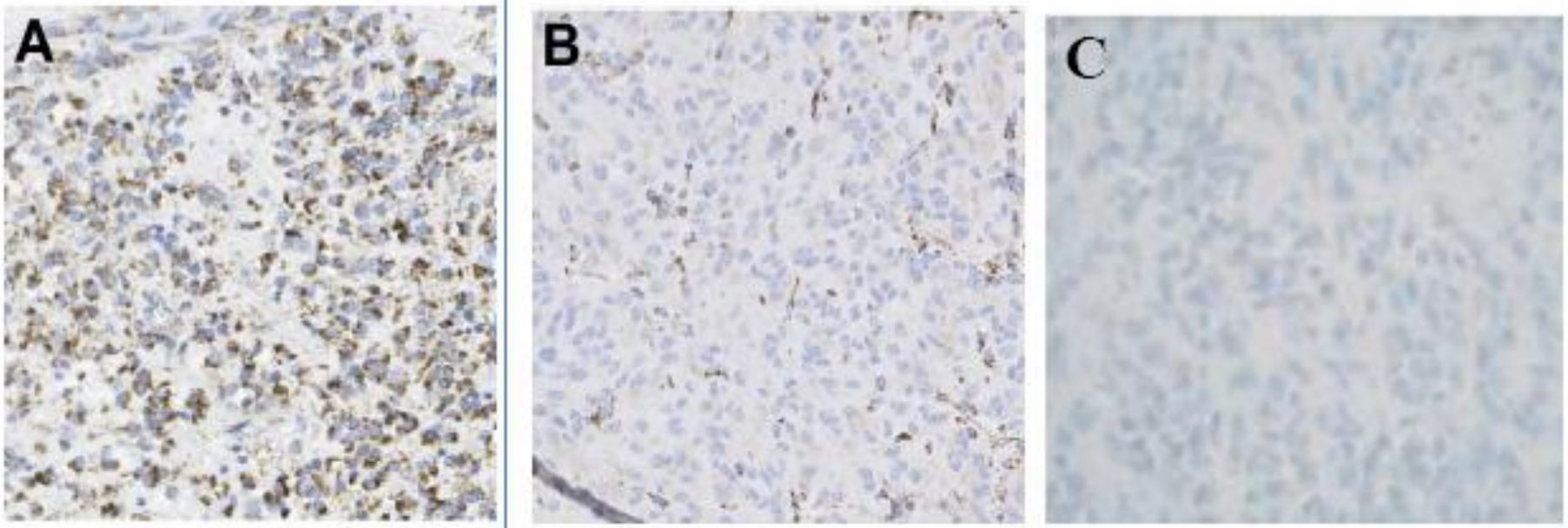


MODERN PATHOLOGY (2010), 1–5

SDHB immunohistochemistry: a useful tool in the diagnosis of Carney–Stratakis and Carney triad gastrointestinal stromal tumors

KIT mutant GIST

'wild-type' GIST



Mod Pathol. 24(1):147-51, 2011

Molecular Subtypes of *KIT/PDGFRA* Wild-Type Gastrointestinal Stromal Tumors

JAMA Oncol. 2016;2(7):922-928

A Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic

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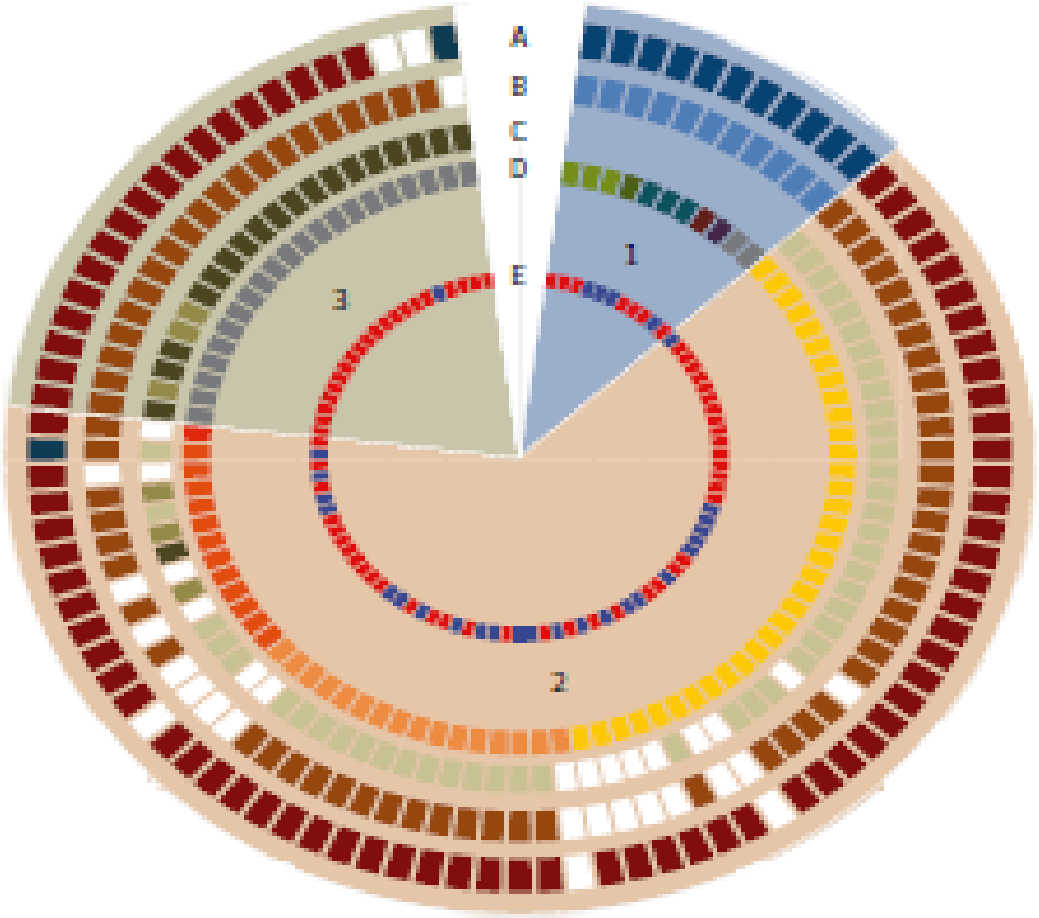
Wild-type GIST specimens from 95 patients (median age, 23 [range, 7-78] years; 70% female). Of SDH-deficient tumors, 63 (67%) had SDH mutations, and in 31 of 38 (82%), the SDHx mutation was also present in germline. Twenty-one (22%) SDH-deficient tumors had methylation of the *SDHC* promoter leading to silencing of expression. Mutations in known cancer-associated pathways were identified in 9 of 11 SDH-competent tumors. Among patients with SDH-mutant tumors, 62% were female, median age was 23 (7-58) years, and approximately 30% presented with metastases (liver, peritoneal, lymph node).

SDHC-epimutant tumors mostly affected young females (20 of 21; median [range] age, 15 years), and approximately 40% presented with metastases (liver, peritoneal, lymph node). SDH-deficient tumors occurred only in the stomach and had an indolent course.

Figure. Immunohistochemical Analysis (IHC) and Genetic Characteristics of Tumors From 95 Patients With *KIT/PDGFRA* Wild-Type Gastrointestinal Stromal Tumors



Groups
1 Normal SDHB expression
2 SDHB mutation
3 SDHC promoter methylation[a]

Circles
A. SDHB IHC: Present; Absent
B. Tumor global methylation: Centile; Deviation
C. Tumor SDHC methylation zygosity: Homozygous; Hemimethylated; Not found
D. Mutations[b]: NF1; CBL; BRAF; ARID1A; KIT/PDGFRA fusion; SDHA; SDHB; SDHC; SDHD; None
E. Sex: Male; Female; Missing Information

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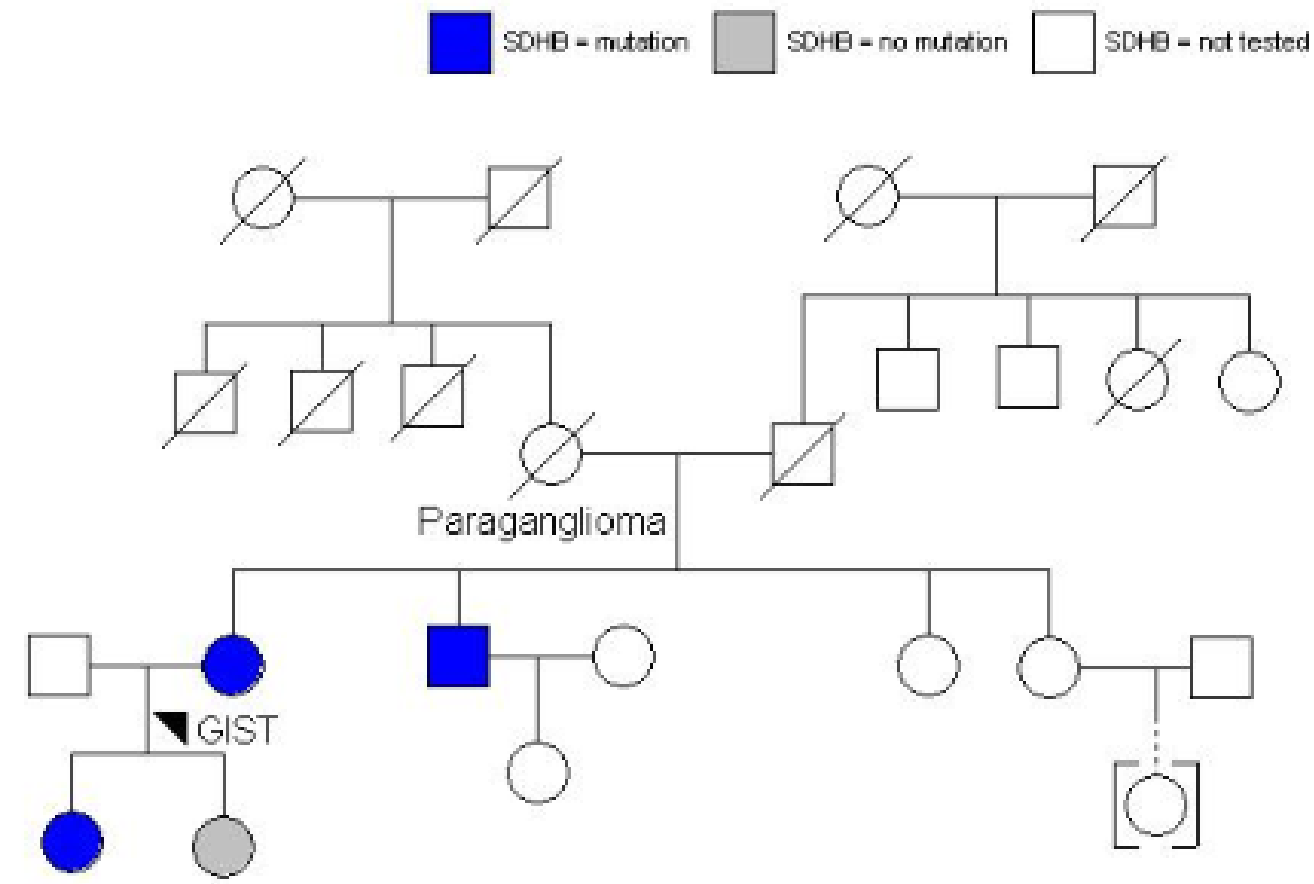
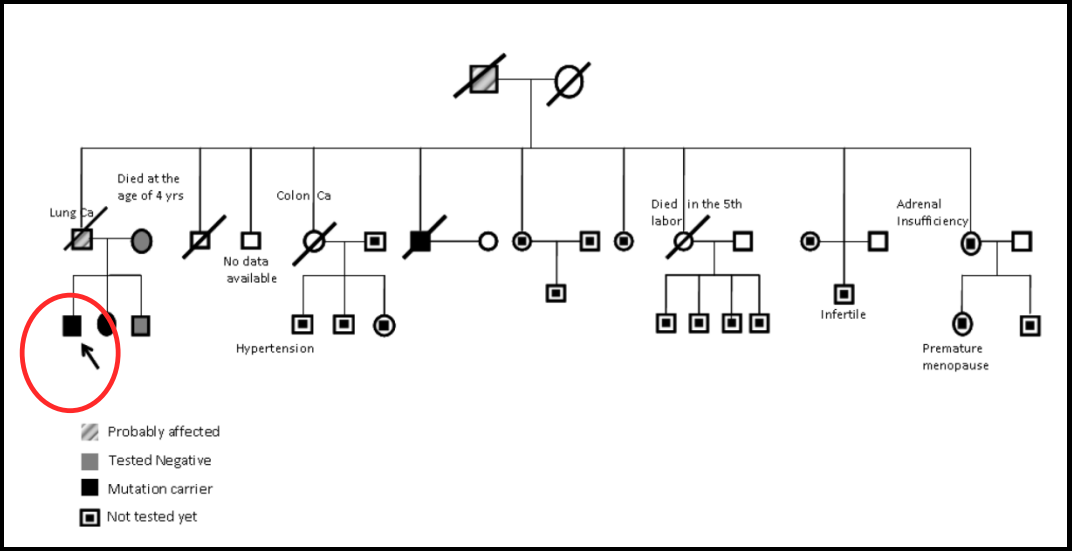
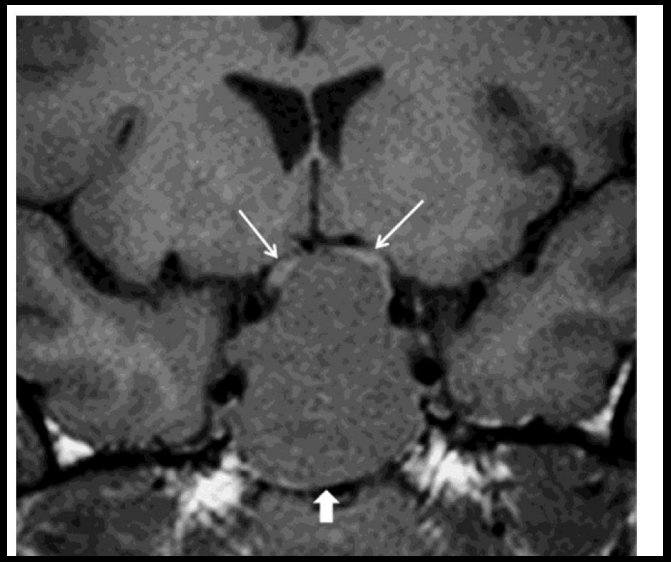
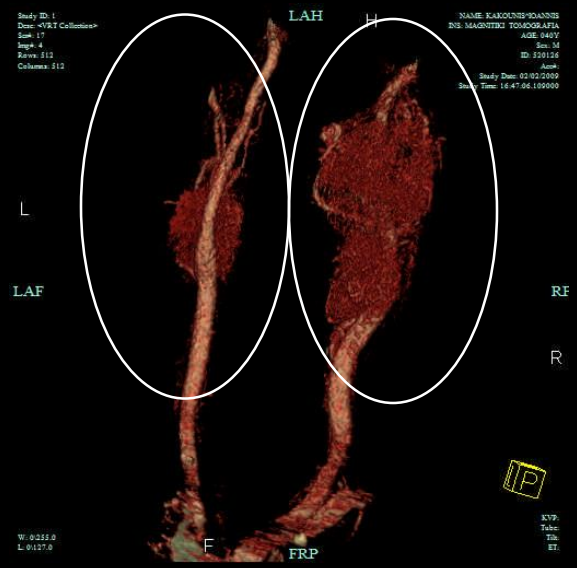
SDHx Defects in GISTs, the NIH GIST clinic data (2008-2018): Other family members

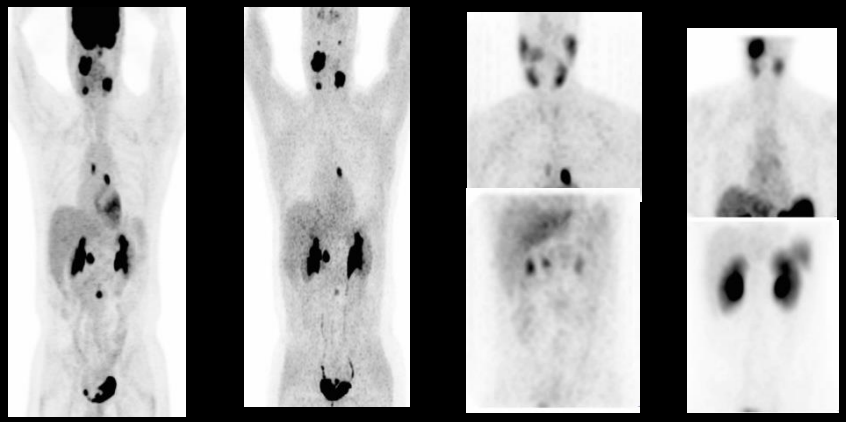






Xekouki P, et al. Succinate dehydrogenase (SDH) D subunit (SDHD) inactivation in a growth-hormone-producing pituitary tumor: A new association for SDH? *J Clin Endocrinol Metab. 97(3):E357-66, 2012*

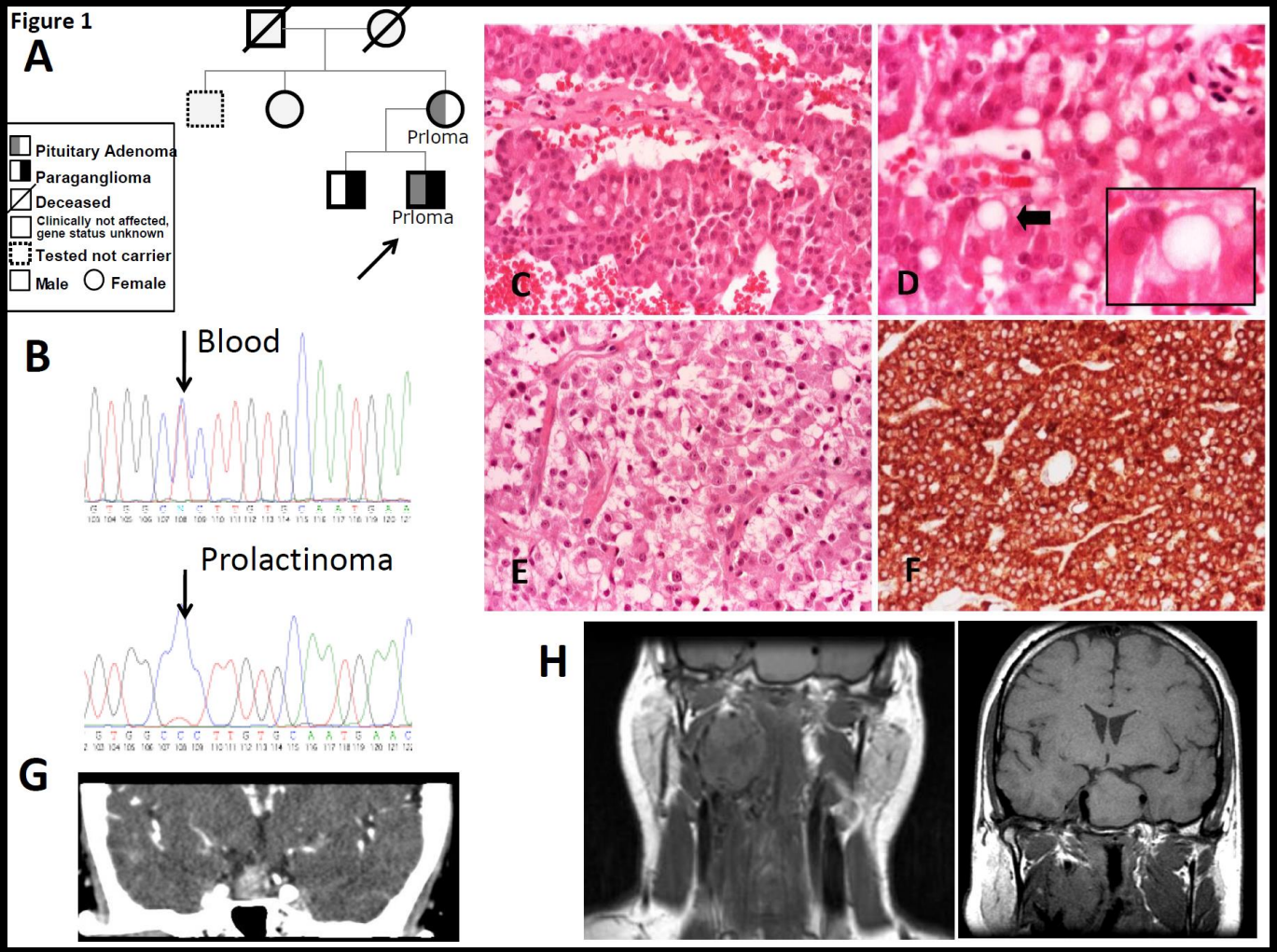




FDG-PET F-Dopa-PET MIBG OCTREOSCAN

C. A. Stratakis NICHD, NIH

Xekouki P & CA Stratakis. Succinate dehydrogenase (SDHx) mutations in pituitary tumors: could this be a new role for mitochondrial complex II and/or Krebs cycle defects? *Endocr Relat Cancer. 19(6):C33-40, 2012*



Dénes et al. 2014 (in submission)

39 patients with familial pituitary adenoma and pheo/PGL

Pituitary adenomas due to *SDH* mutations have unique histology: intracytoplasmic vacuoles and other features

Concluding remarks

Mutations of the *SDHA*, *SDHB*, *SDHC* and *SDHD* genes are frequent in non-KIT/non-PDGFRA-mutant GISTs; these mutations are also the cause of the familial GIST/PGL syndrome (CSS), but not every patient with an SDHx mutation has CSS. SDHB-negative immunoreactivity is the hallmark of these lesions regardless of the SDHx-subunit mutation.

Together, CSS and SDHx-mutant GISTs constitute about 15% of the so called "wild-type" GISTs; additional mitochondrial oxidation defects account for the remaining as is suggested by decreased complex-II activity and low immunostaining for (expression of) SDHB.

SDHx defects, in addition to PGL/PHEOs, GISTs, thyroid & renal cancer, rarely predispose to pituitary tumors.

Hypothesis: Deficient mitochondrial oxidation, which in turn activates oncogenic (i.e. KIT, HIFa) pathways, has a wide role in endocirne tumorigenesis.

the NIH Pediatric & Wildtype GIST Clinic

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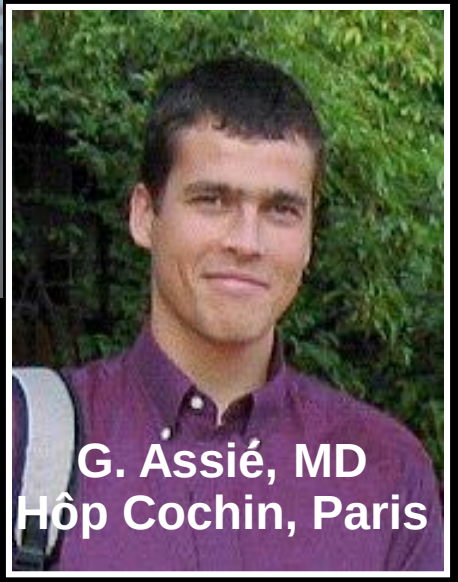

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