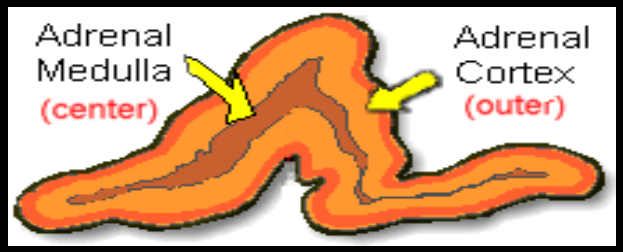
Ενδοραμα 2018: Επινεφριδια

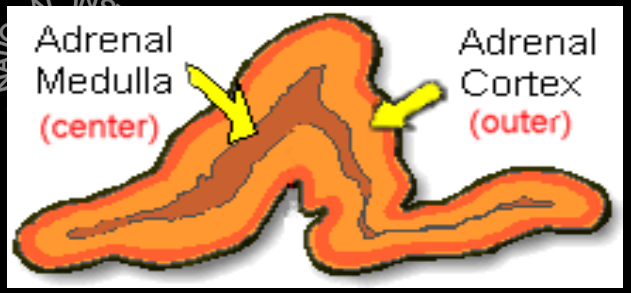
Κωστης Α. Στρατακης

Πατρα, 26–27 Ιανουαριου 2018

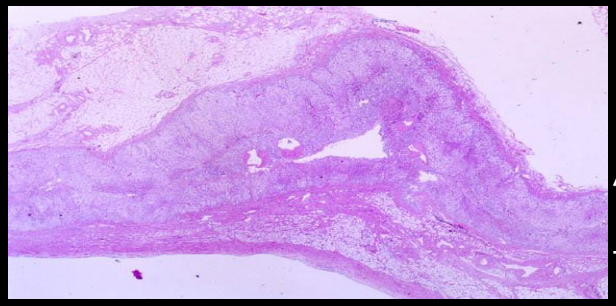
Section on Endocrinology & Genetics,
National Institute of Child Health & Human Development,
National Institutes of Health

Scientific Director , NICHD, NIH





Histopathology: adrenal

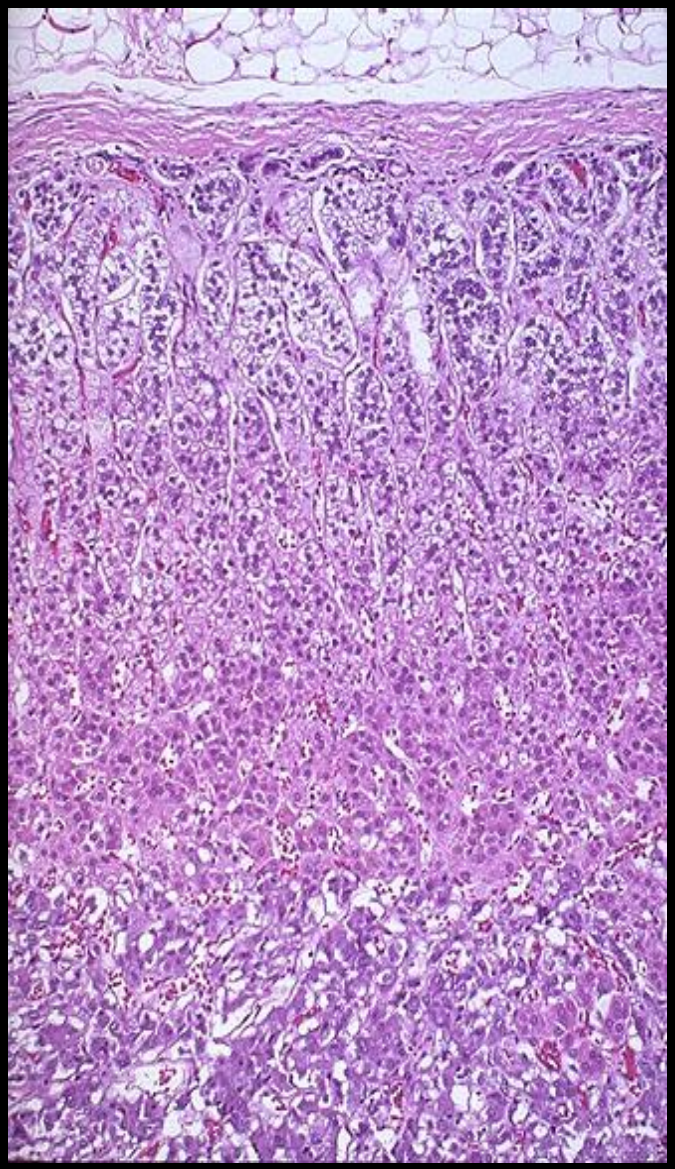


capsule

zona glomerulosa

zona fasciculata

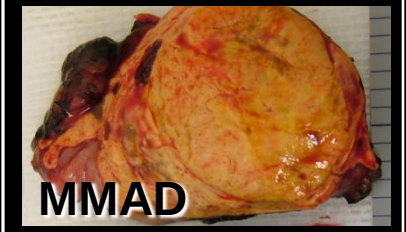
zona reticularis



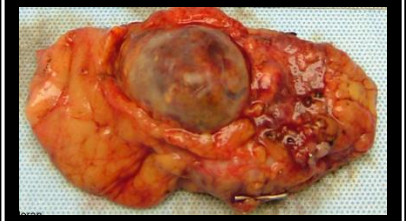
ADRENAL 2007-2017

1. The PKA pathway and benign cortisol-producing lesions
2. Mass-spec (LC/MS): the new frontier in steroid production
3. Adrenocortical hypoplasia and development: beyond CAH and SF1!
4. ARMC5 and the adrenal: a new gene and the disease that is inherited
5. Food-dependent Cushing syndrome: the new genetics
6. Aldosterone-producing lesions; from KCNJ5 and beyond
7. Subclinical everything: hypo/hyper aldo+cortisol, adrenal fatigue
8. Adrenocortical cancer: new genetics; after mitotane what?
9. Succinate dehydrogenase (SDH) mutations: not only pheochromocytomas!
10. The other (non-SDH) genes in pheochromocytoma/paraganglioma

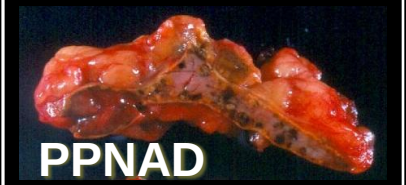
Genetic causes of adrenal hyperplasias: protein kinase A and related defects



Macronodular

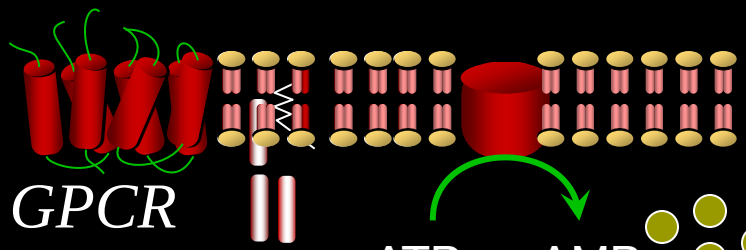


Nodular

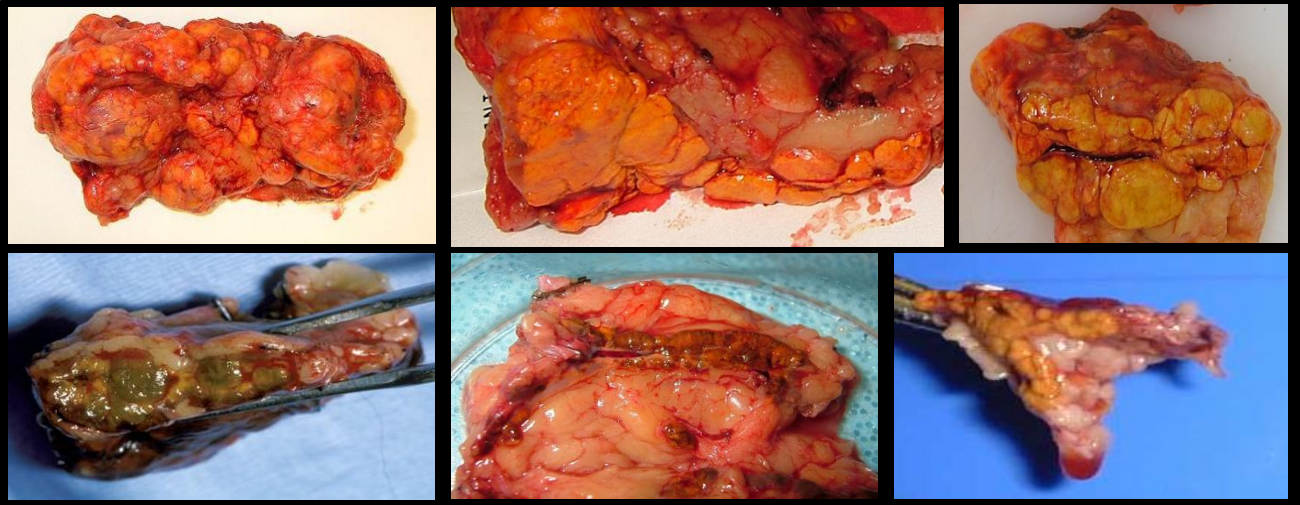


Micronodular

Bilateral Adrenocortical Hyperplasias



Bilateral adrenocortical hyperplasias
are genetically heterogeneous disorders
with a range of phenotypes (pheno- and genocopies)



J Clin Endocrinol Metab, December 2011, 96(12):3775–3784

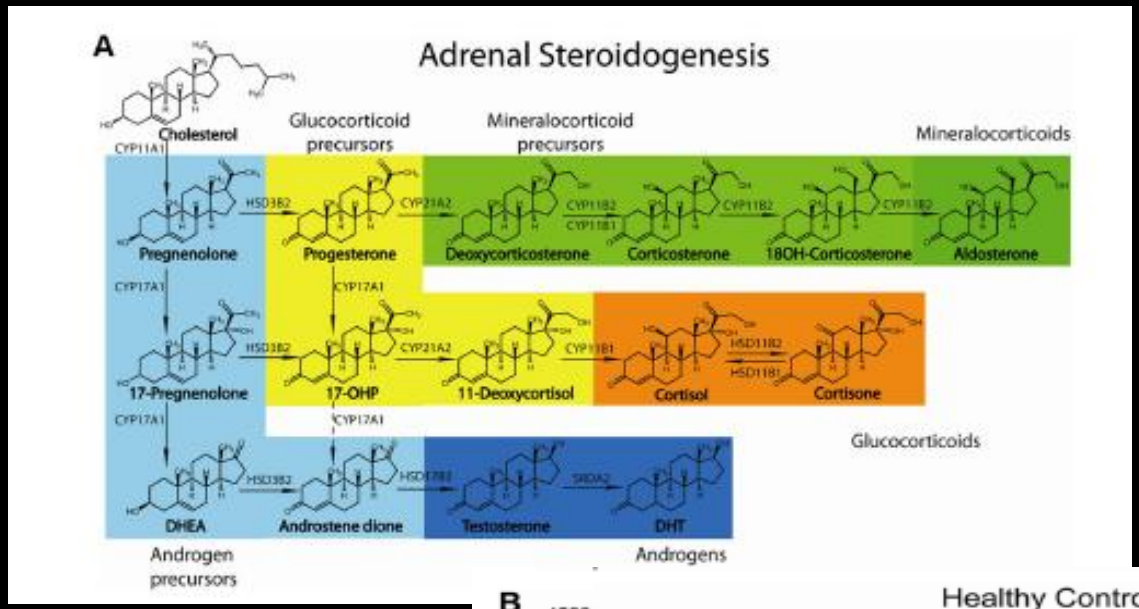
Urine Steroid Metabolomics as a Biomarker Tool for Detecting Malignancy in Adrenal Tumors

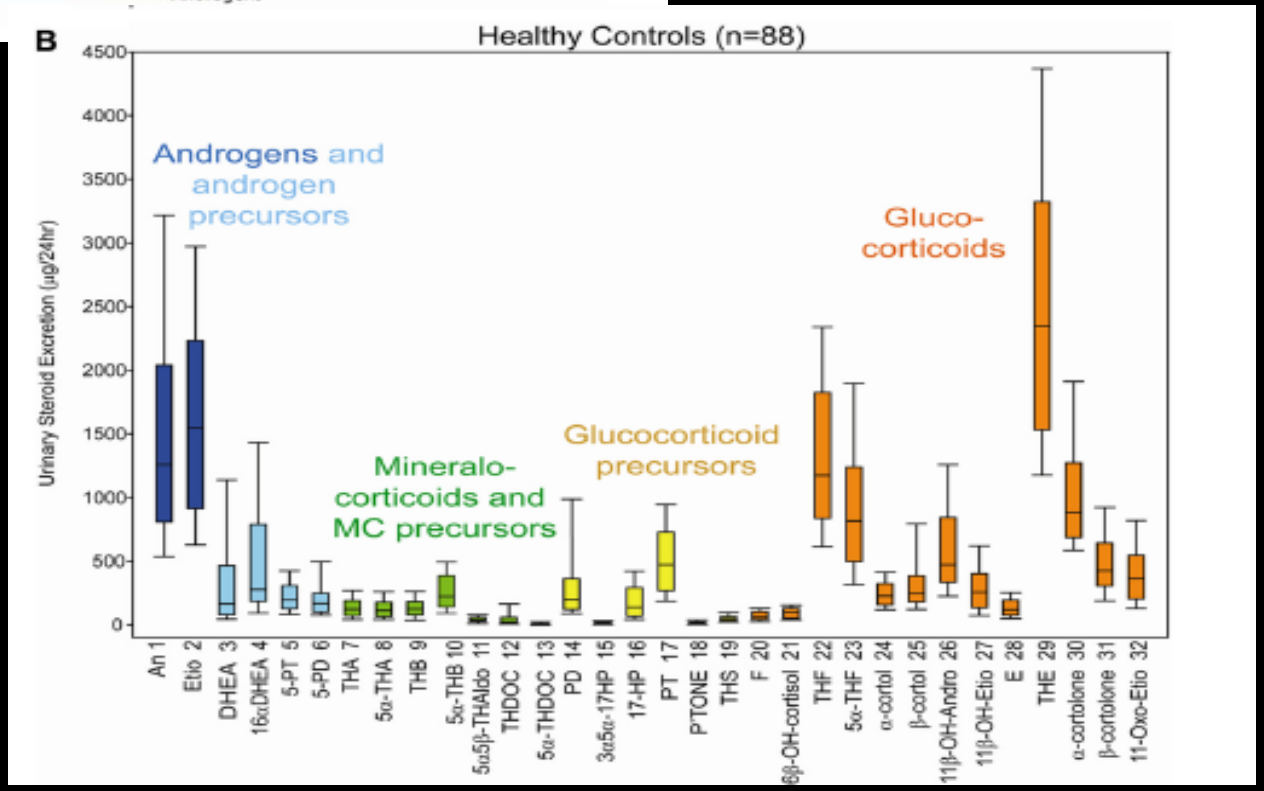
Wiebke Arlt, Michael Biehl, Angela E. Taylor, Stefanie Hahner, Rossella Libé, Beverly A. Hughes, Petra Schneider, David J. Smith, Han Stiekema, Nils Krone, Emilio Porfiri, Giuseppe Opocher, Jerôme Bertherat, Franco Mantero, Bruno Allolio, Massimo Terzolo, Peter Nightingale, Cedric H. L. Shackleton, Xavier Bertagna, Martin Fassnacht, and Paul M. Stewart

Design: Quantification of 32 distinct adrenal derived steroids was carried out by gas chromatography/mass spectrometry in 24-h urine samples from 102 ACA patients (age range 19–84 yr) and 45 ACC patients (20–80 yr). Underlying diagnosis was ascertained by histology and metastasis in ACC and by clinical follow-up [median duration 52 (range 26–201) months] without evidence of metastasis in ACA. Steroid excretion data were subjected to generalized matrix learning vector quantization (GMLVQ) to identify the most discriminative steroids.

Results: Steroid profiling revealed a pattern of predominantly immature, early-stage steroidogenesis in ACC. GMLVQ analysis identified a subset of nine steroids that performed best in differentiating ACA from ACC. Receiver-operating characteristics analysis of GMLVQ results demonstrated sensitivity = specificity = 90% (area under the curve = 0.97) employing all 32 steroids and sensitivity = specificity = 88% (area under the curve = 0.96) when using only the nine most differentiating markers.

Conclusions: Urine steroid metabolomics is a novel, highly sensitive, and specific biomarker tool for discriminating benign from malignant adrenal tumors, with obvious promise for the diagnostic work-up of patients with adrenal incidentalomas. (*J Clin Endocrinol Metab* 96: 3775–3784, 2011)


A
Adrenal Steroidogenesis
Cholesterol
Glucocorticoid precursors
Mineralocorticoid precursors
Mineralocorticoids
CYP11A1
Pregnenolone
HSD3B2
Progesterone
CYP21A2
Deoxycorticosterone
CYP11B2
CYP11B1
Corticosterone
CYP11B2
18OH-Corticosterone
CYP11B2
Aldosterone
CYP17A1
17-Pregnenolone
HSD3B2
17-OHP
CYP17A1
CYP21A2
11-Deoxycortisol
CYP11B1
Cortisol
HSD11B2
HSD11B1
Cortisone
Glucocorticoids
CYP17A1
DHEA
HSD3B2
Androstene dione
HSD17B3
Testosterone
SRDA2
DHT
Androgen precursors
Androgens


B
Healthy Controls (n=88)
Urinary Steroid Excretion (µg/24hr)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Androgens and androgen precursors
Mineralo-corticoids and MC precursors
Glucocorticoid precursors
Gluco-corticoids
An 1
Etio 2
DHEA 3
16α-DHEA 4
5-PT 5
5-PD 6
THA 7
5α-THA 8
THB 9
5α-THB 10
5α5β-THAldo 11
THDOC 12
5α-THDOC 13
PD 14
3α5α-17HP 15
17-HP 16
PT 17
PTONE 18
THS 19
F 20
6β-OH-cortisol 21
THF 22
5α-THF 23
α-cortol 24
β-cortol 25
11β-OH-Andro 26
11β-OH-Etio 27
E 28
THE 29
α-cortolone 30
β-cortolone 31
11-Oxo-Etio 32

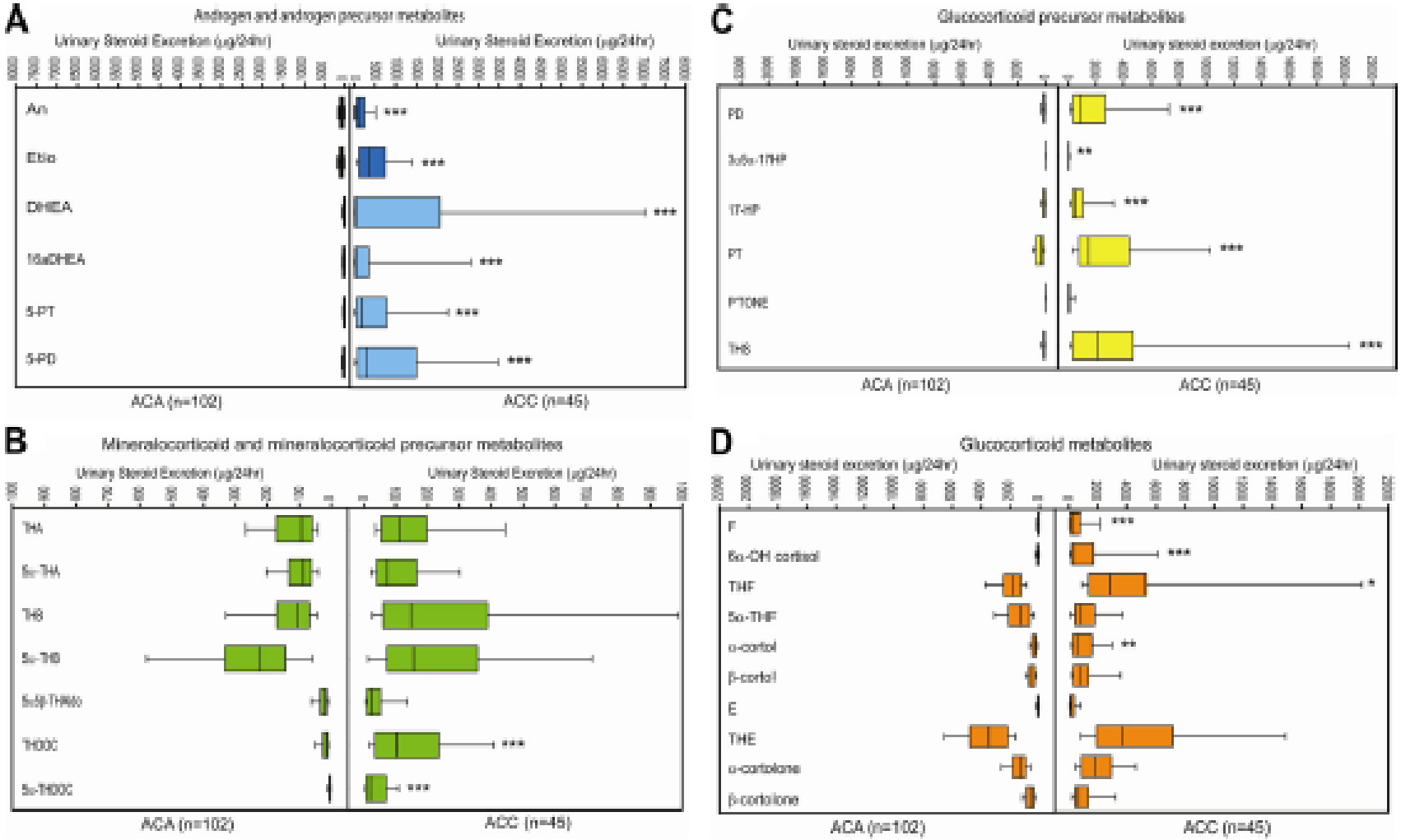
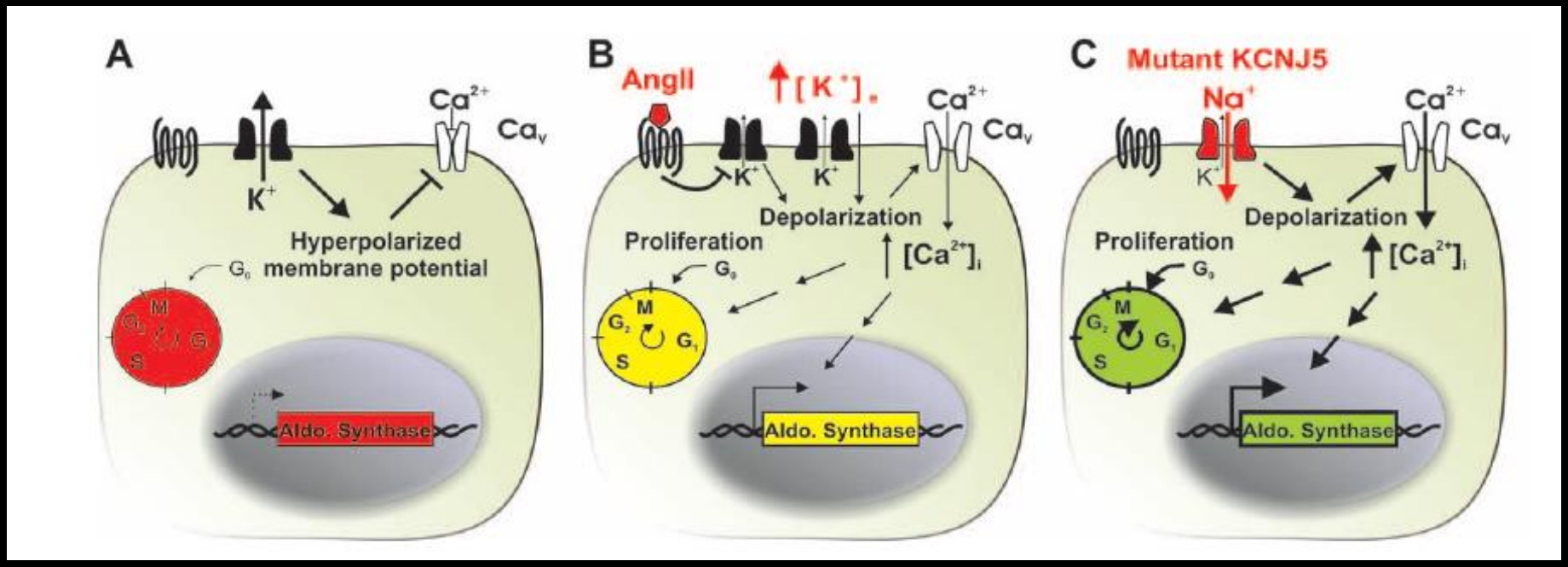


FIG. 2. Steroid metabolite excretion in ACA (n = 102) and ACC (n = 45) according to steroid classes. A, Metabolites of adrenal androgen precursors and active androgens; B, metabolites of mineralocorticoids and their precursors; C, metabolites of glucocorticoid precursors; D, cortisol and cortisone metabolites. Box plots represent median and interquartile ranges; the whiskers represent 5th and 95th percentile, respectively. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ comparing ACA with ACC.

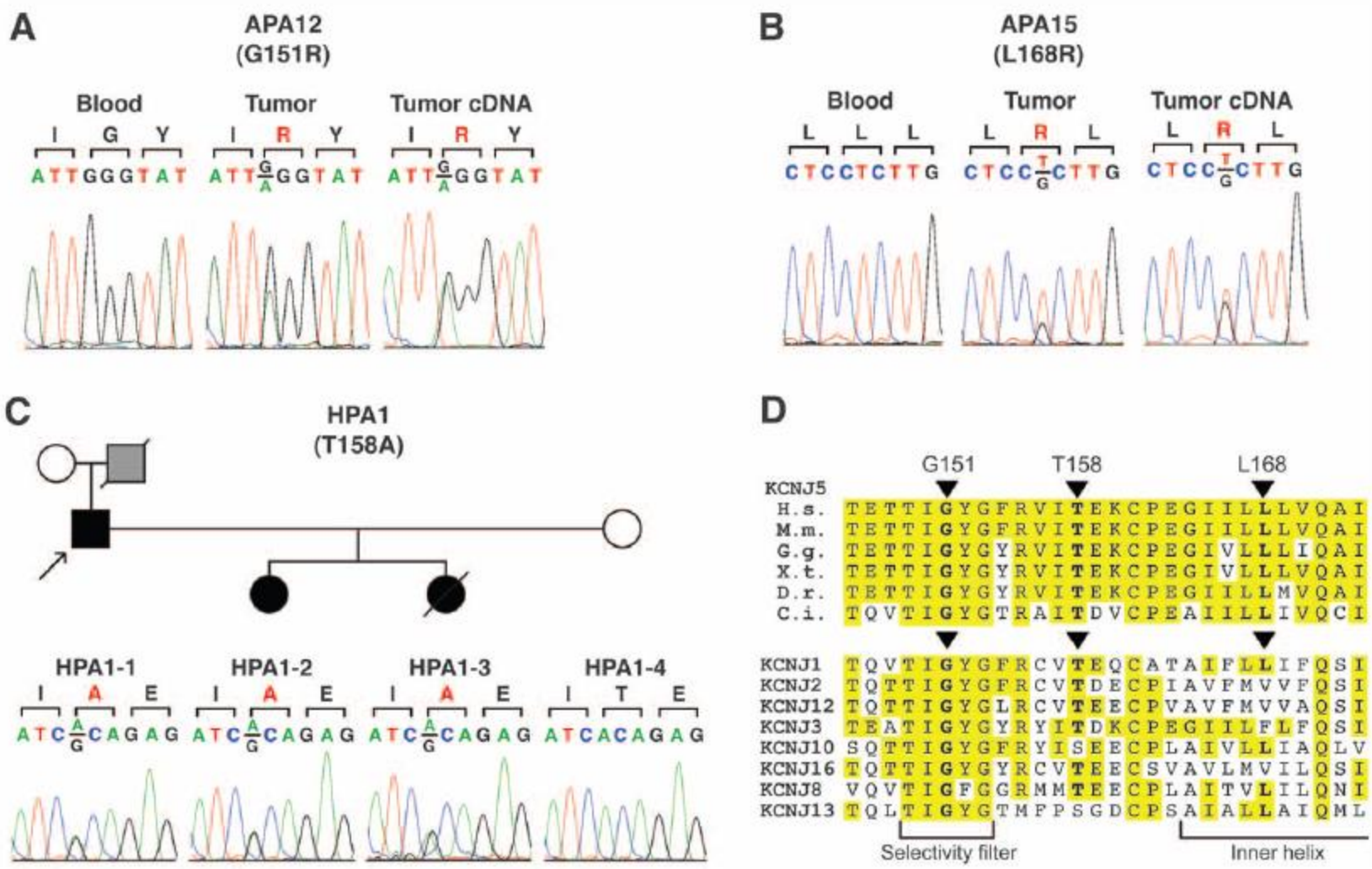
K^+ Channel Mutations in Adrenal Aldosterone-Producing Adenomas and Hereditary Hypertension

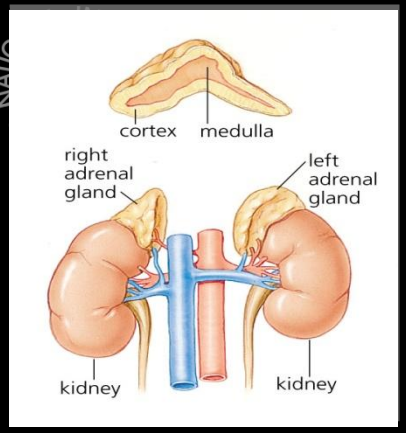
11 FEBRUARY 2011 VOL 331 **SCIENCE**

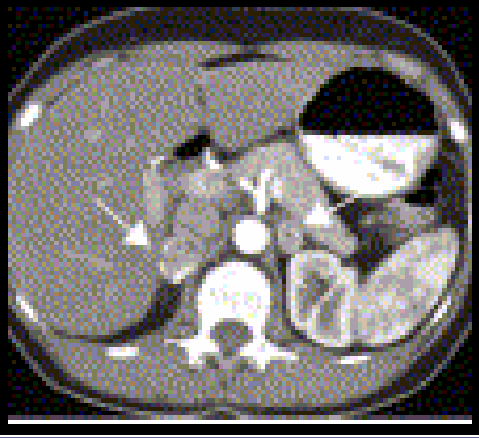
Murim Choi,[1] Ute I. Scholl,[1] Peng Yue,[2*] Peyman Björklund,[3,4*] Bixiao Zhao,[1*] Carol Nelson-Williams,[1] Weizhen Ji,[1] Yoonsang Cho,[5] Aniruddh Patel,[1] Clara J. Men,[1] Elias Lolis,[5] Max V. Wisgerhof,[6] David S. Geller,[7] Shrikant Mane,[8] Per Hellman,[4] Gunnar Westin,[4] Göran Åkerström,[4] Wenhui Wang,[2] Tobias Carling,[3] Richard P. Lifton[1†]

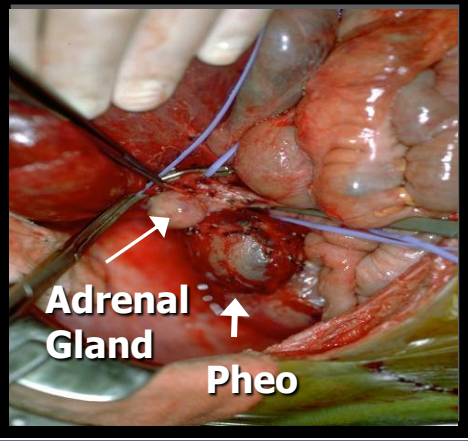


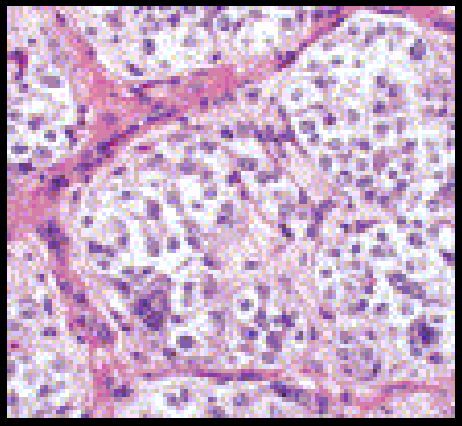
11 FEBRUARY 2011 VOL 331 **SCIENCE**











Inherited Pheochromocytoma Syndromes

Multiple Endocrine Neoplasia type 2

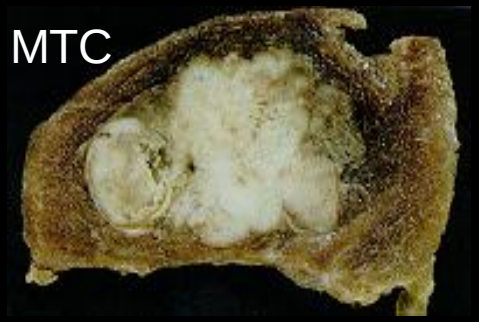
-RET proto-oncogene

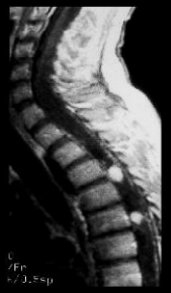
Von Hippel-Lindau D. & NF1

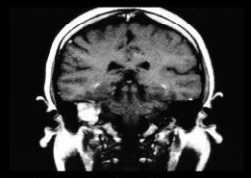
-VHL, NF1 tumor suppressors

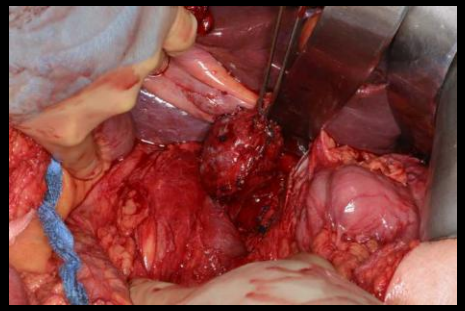
Paraganglioma Syndromes

-SDHB, SDHC, SDHD, CTR/D




Hemangioblastoma Spinal Cord


Endolymphatic Sac Tumor

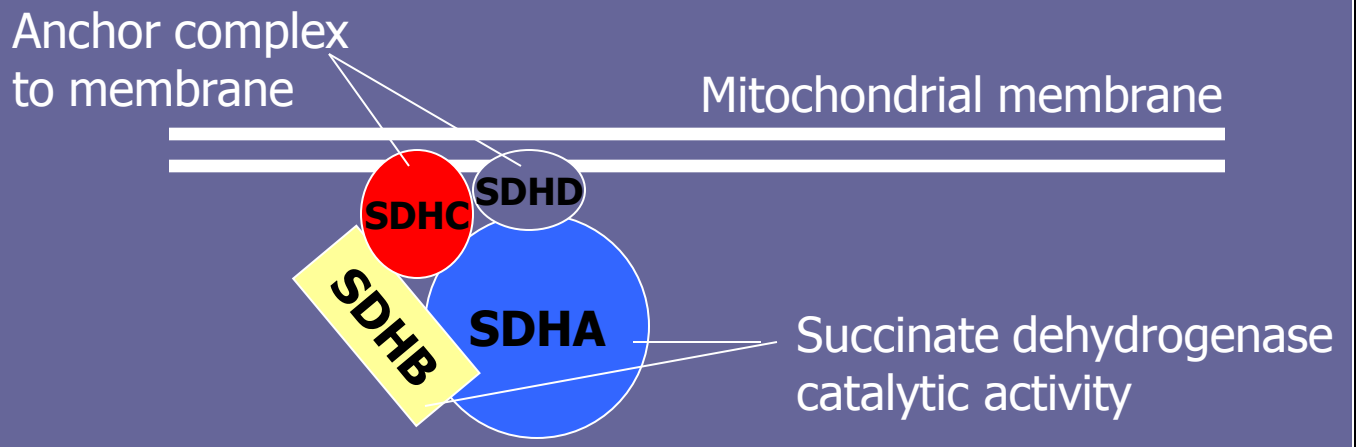


Genetic Defects in PGLs

PGL1 - *SDHD* 11q23
PGL3 - *SDHC* 1q21.2
PGL4 - *SDHB* 1p36
PGL2 - *SDHA* 5q

Mitochondrial Complex II

Succinate dehydrogenase
Four subunits, SDHA-SDHD
Key function in energy production

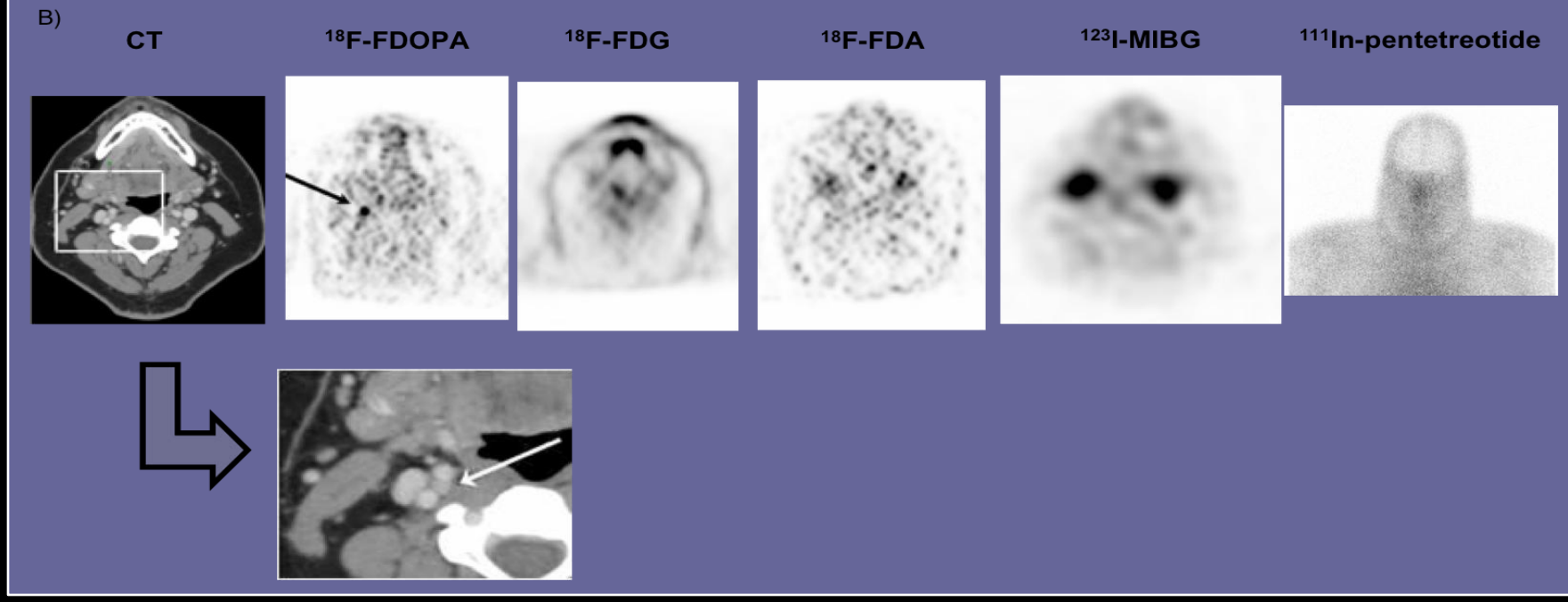


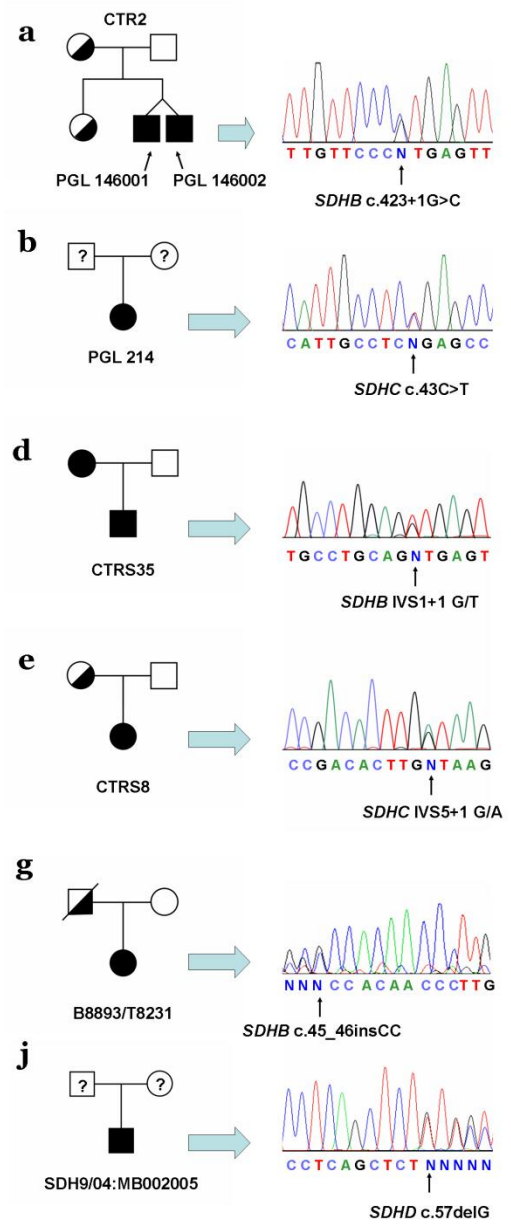
VOLUME 29 · NUMBER 31 · NOVEMBER 1 2011

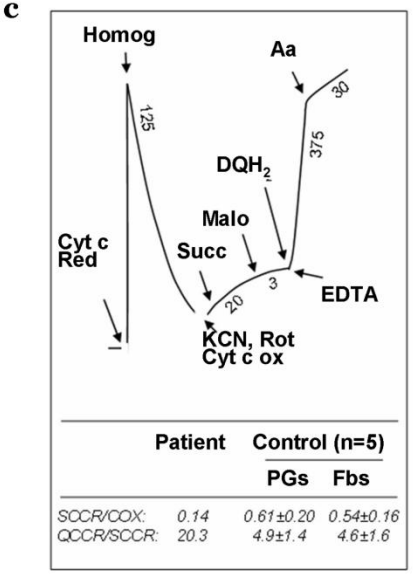
JOURNAL OF CLINICAL ONCOLOGY

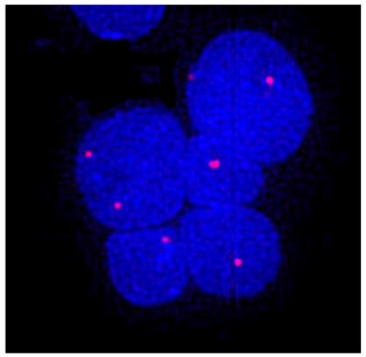
Metastatic Pheochromocytoma/Paraganglioma Related to Primary Tumor Development in Childhood or Adolescence: Significant Link to *SDHB* Mutations

Kathryn S. King, Tamara Prodanov, Vitaly Kantorovich, Tito Fojo, Jacqueline K. Hewitt, Margaret Zacharin, Robert Wesley, Maya Lodish, Margarita Raygada, Anne-Paule Gimenez-Roqueplo, Shana McCormack, Graeme Eisenhofer, Dragana Milosevic, Electron Kebebew, Constantine A. Stratakis, and Karel Pacak









The PGL+GIST syndrome (dyad)

Mutations of the *SDHB*, *SDHC* and *SDHD* genes in patients with the dyad, the syndrome of PGL and GISTs

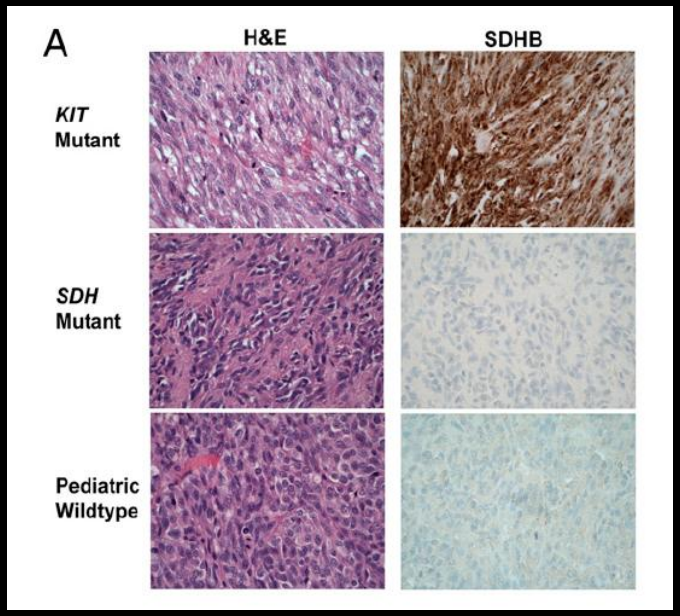
N. Engl. J. Med. (2007)

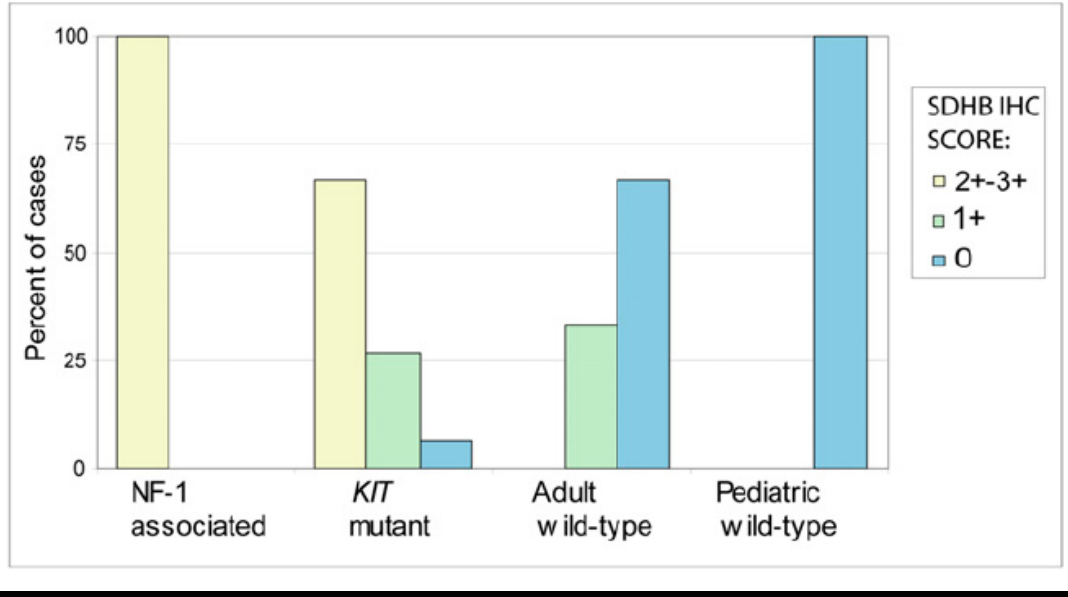
Eur. J. Hum. Genet. (2007)

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]

314–318 | PNAS | January 4, 2011 | vol. 108 | no. 1





Paragangliomatosis Associated With Multiple Endocrine Adenomas

Farbood Farhi, MD; Steven H. Dikman, MD; William Lawson, MD, DDS;
Rhoda H. Cobin, MD; Frederick G. Zak, MD

Arch Pathol Lab Med—Vol 100, Sept 1976

Succinate dehydrogenase (SDH) D subunit (*SDHD*) nactivation in a growth-hormone producing pituitary tumor: a new association for SDH?

Paraskevi Xekouki [1, 2], Karel Pacak[3], Madson Almeida[1], Christopher A Wassif [4], Pierre Rustin[5], Maria Nesterova[1], Maria de la Luz Sierra[1], Joey Matro[3], Evan Ball[1], Monalisa Azevedo[1], Anelia Horvath[1], Charalampos Lyssikatos [1], Martha Quezado [6], Nicholas Patronas[7], Barbara Ferando[8], Barbara Pasini [8], *Aristides Lytras[2,9], *George Tolis[2], & Constantine A. Stratakis [1]

J. Clin. Endocrinol. Metab 2012

ADRENAL 2018-2027

1. Precision medicine in the adrenal
2. Adrenal development, organoids, and adrenal regrowth/replacement
3. Treatment of adrenal cancer
4. Treatment of malignant pheochromocytoma/paraganglioma
5. Medical treatment of adrenal insufficiency
6. Medical treatment of subclinical steroid hypersecretion