Hyperplasie macronodulaire des surrénales : stratégies de recherche de nouveaux gènes de prédisposition

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2017

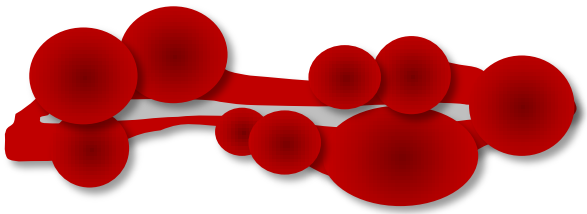
JOURNÉE ANNUELLE
4ème ÉDITION

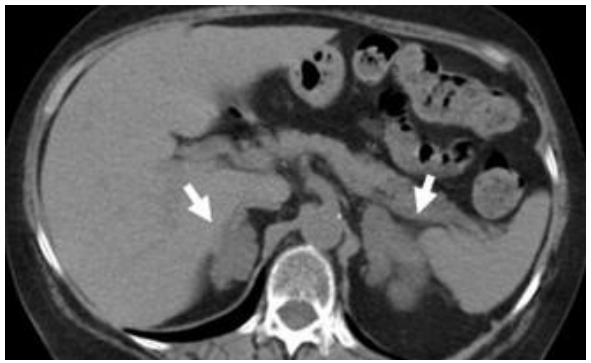
FIRENDO
FILIÈRE MALADIES RARES ENDOCRINIENNES

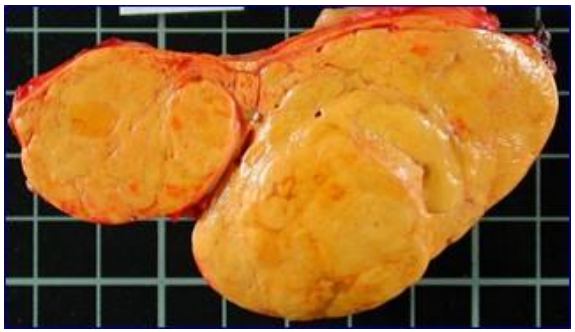
Definition

Bilateral enlargment of both adrenals

Macronodular Hyperplasia

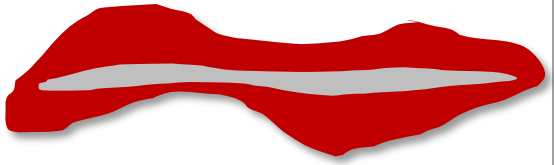


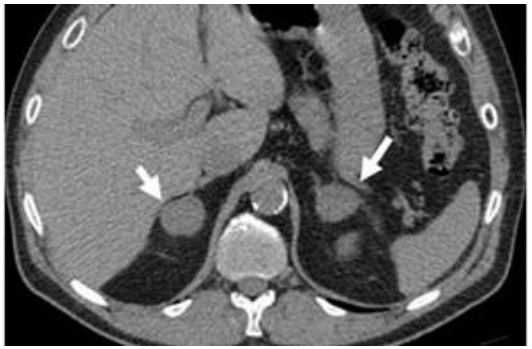


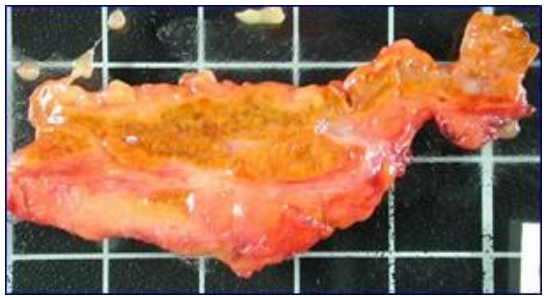


F Tissier

Diffuse Hyperplasia







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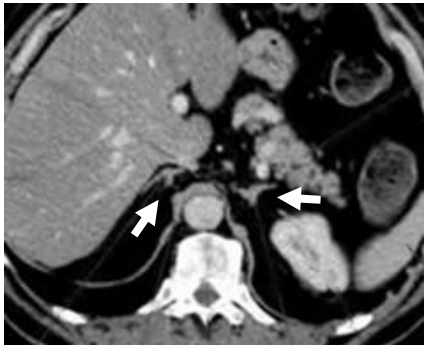
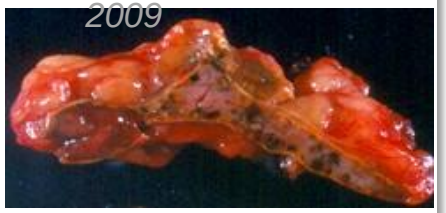
Primary Pigmented Nodular Adrenal Dysplasia



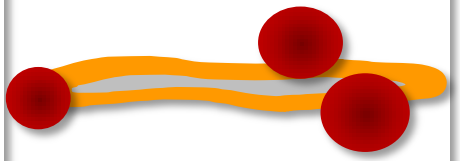
Hsiao, JCEM 2009



Meador et al, JCEM 1967

Carney et al, Medicine 1985

Multiple adenomas

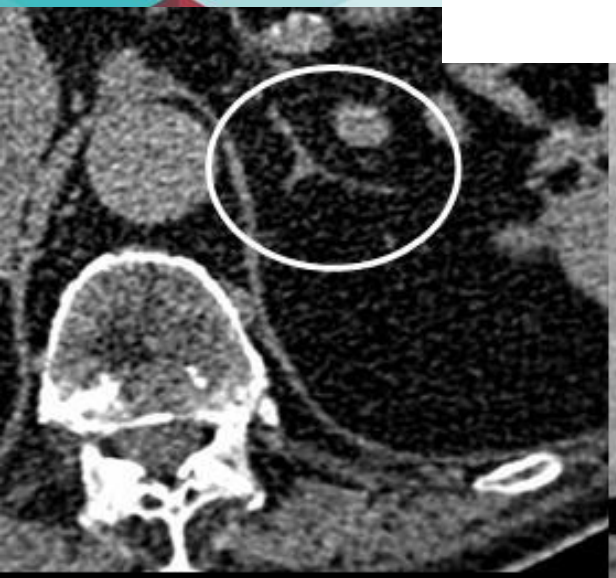


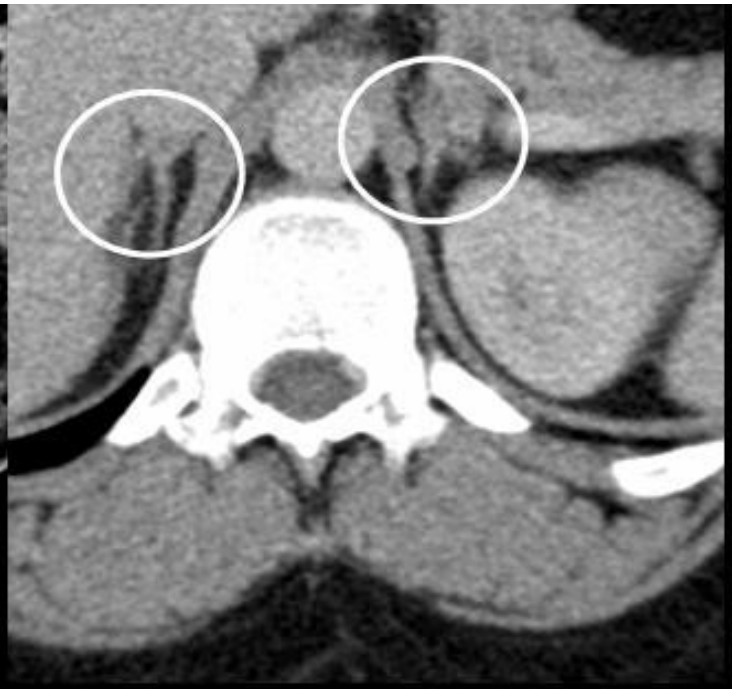
Differential diagnoses

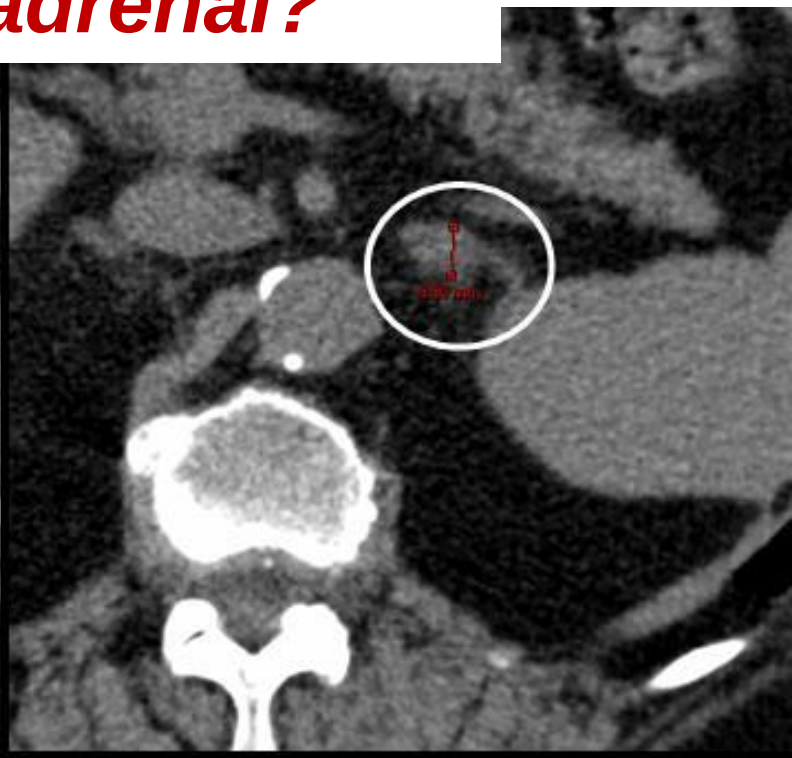
- CAH
- Hemorragia
- Metastases, lymphoma
- Pheo
- ACTH-dpt hypercortisolism

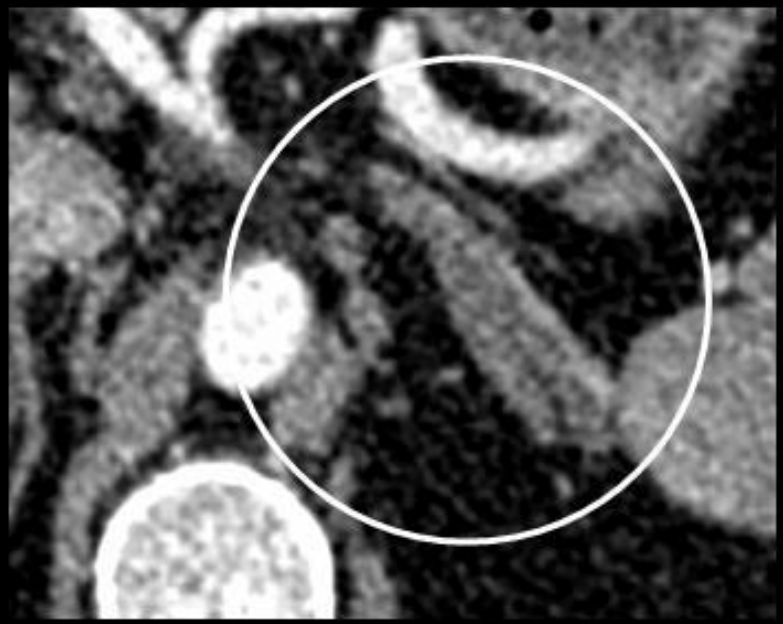
FIRENDO

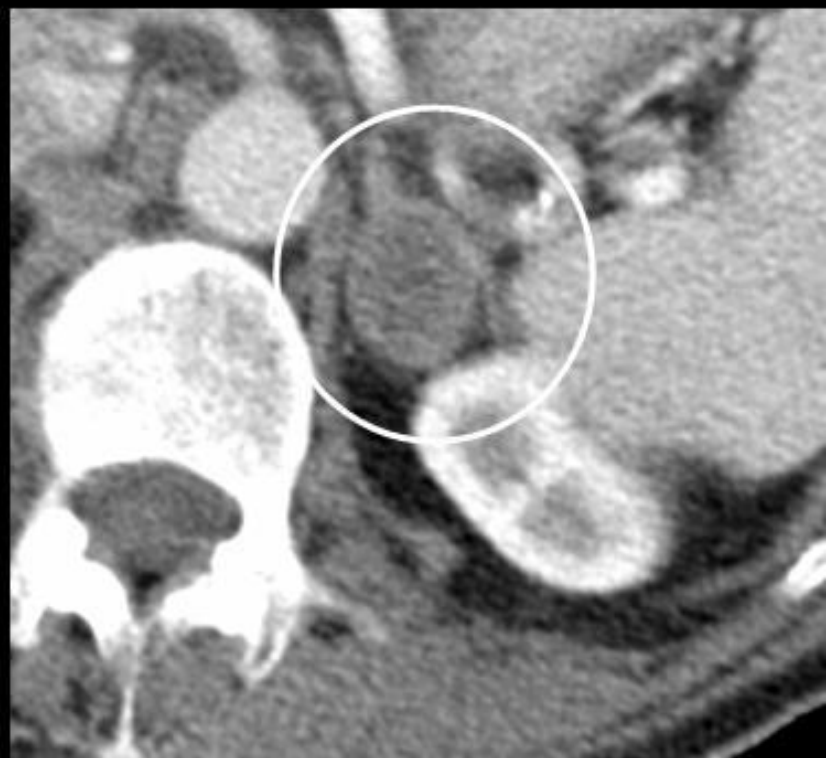
What is a normal adrenal?











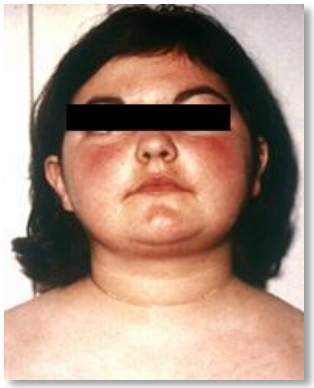
Variable Hypercortisolism
Cushing syndrome

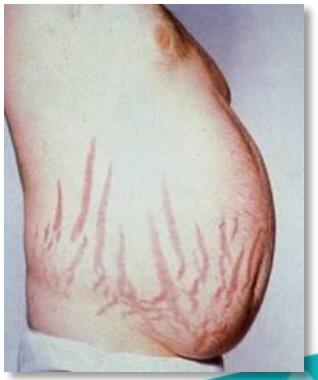
Non-secreting

Subclinical hypercortisolism

Overt hypercortisolism

Hypertension
Diabetes
Osteoporosis
Infarct, Stroke
Thrombo-embolic disease





Prevalence?

- 2% of overt hypercortisolism
- A « significant proportion » of incidentalomas (incidentalomas: 1-5% of population)

The adrenal networks….

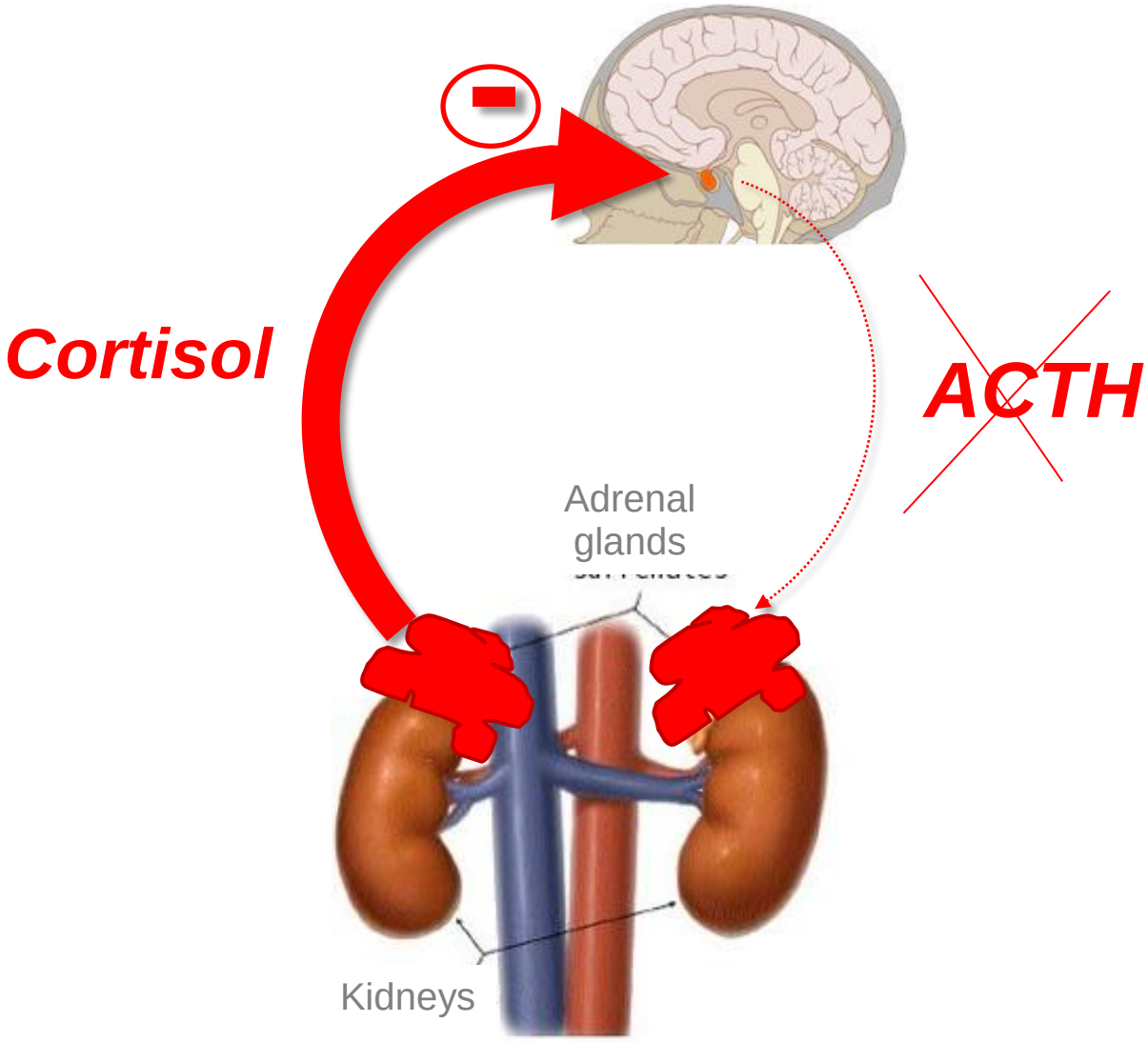
COMETE
Cancers de la surrénale

CCTN

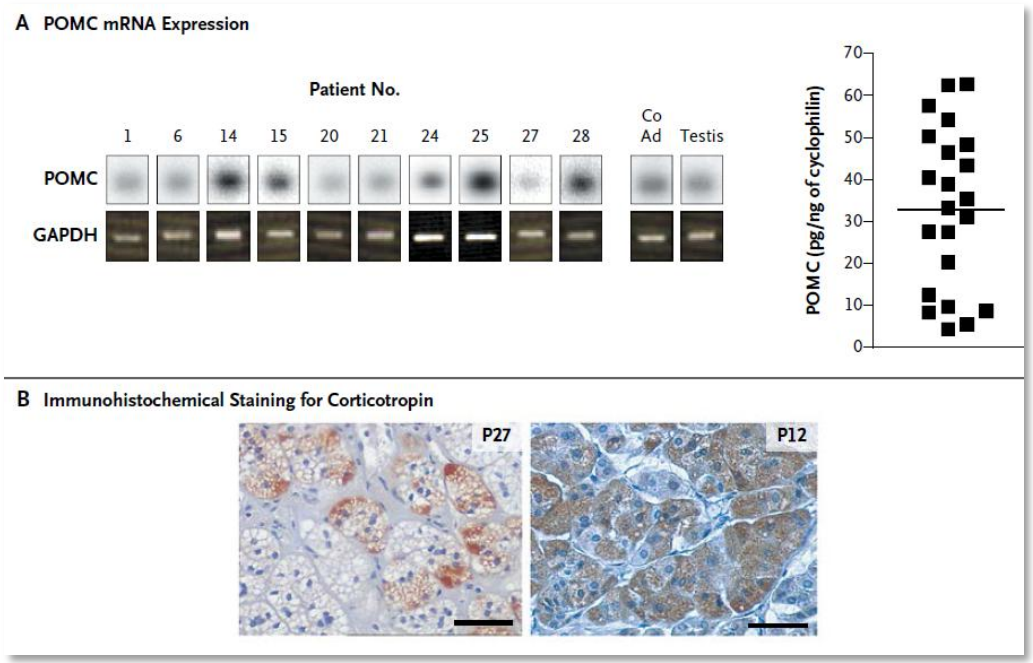
ens@t

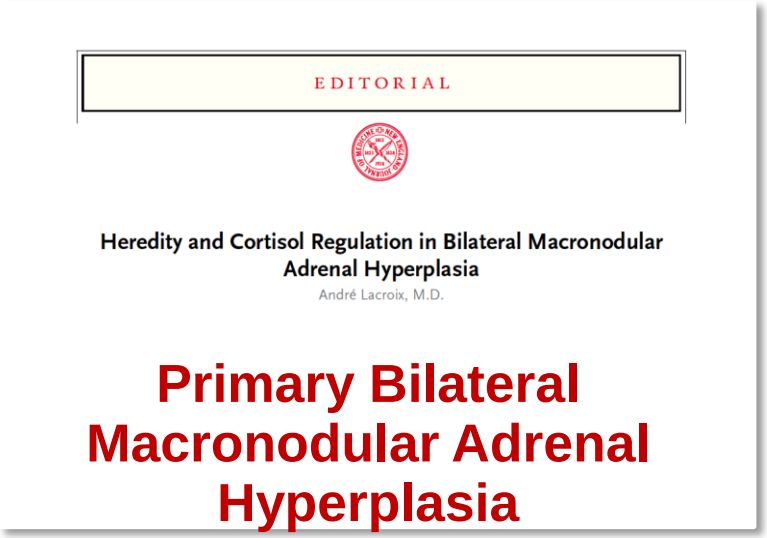
FIRENDO

« ACTH-independant Adrenal Hyperplasia… »



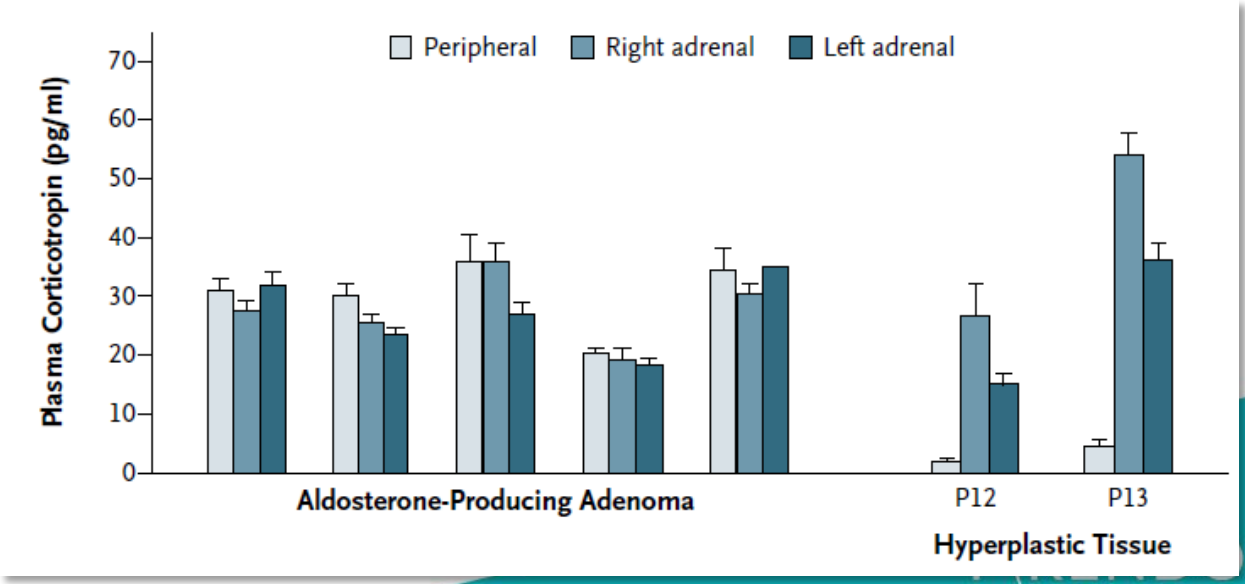
…But is it really « ACTH-independant? »



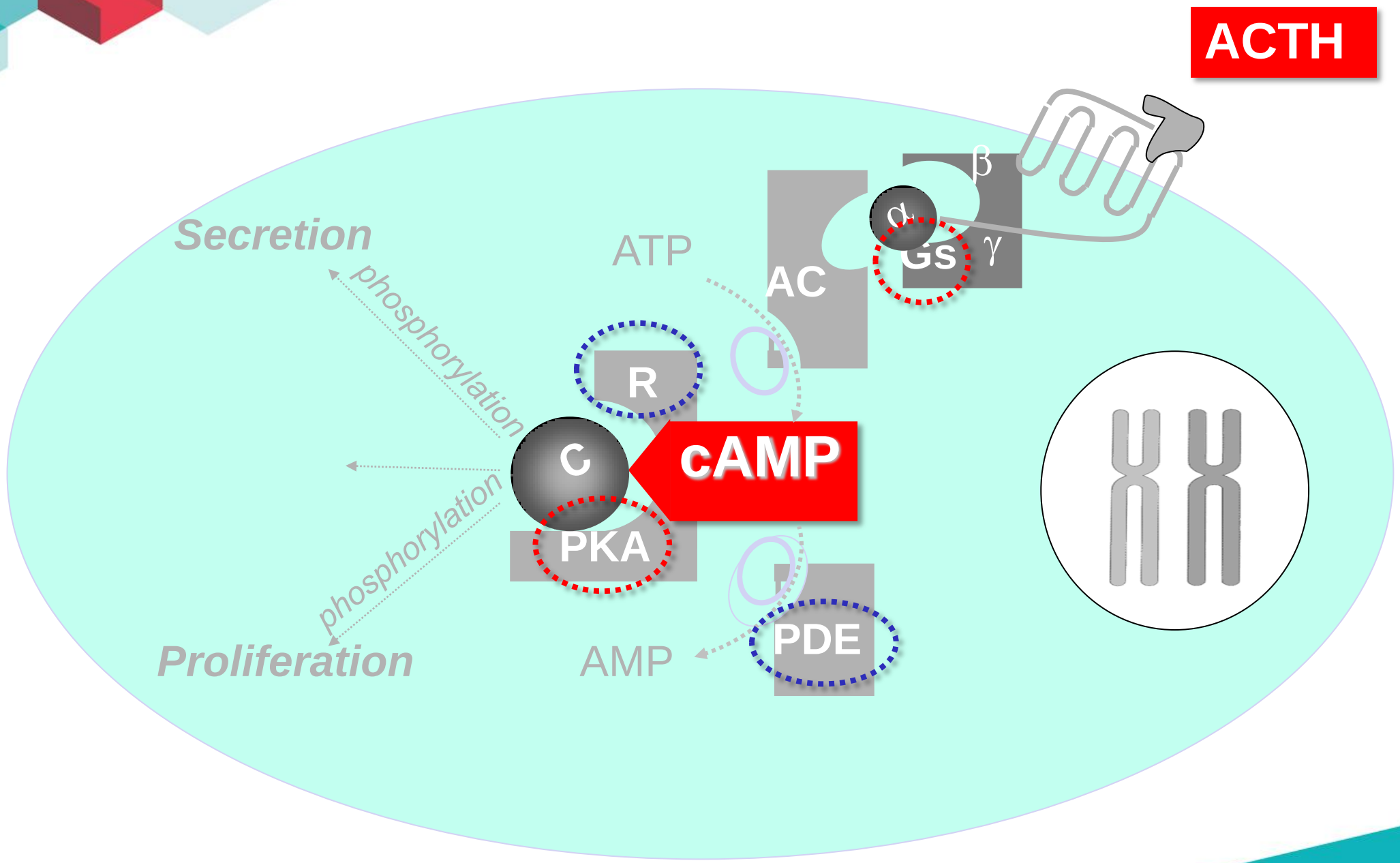


Primary Bilateral Macronodular Adrenal Hyperplasia

Louiset et al., NEJM 2013

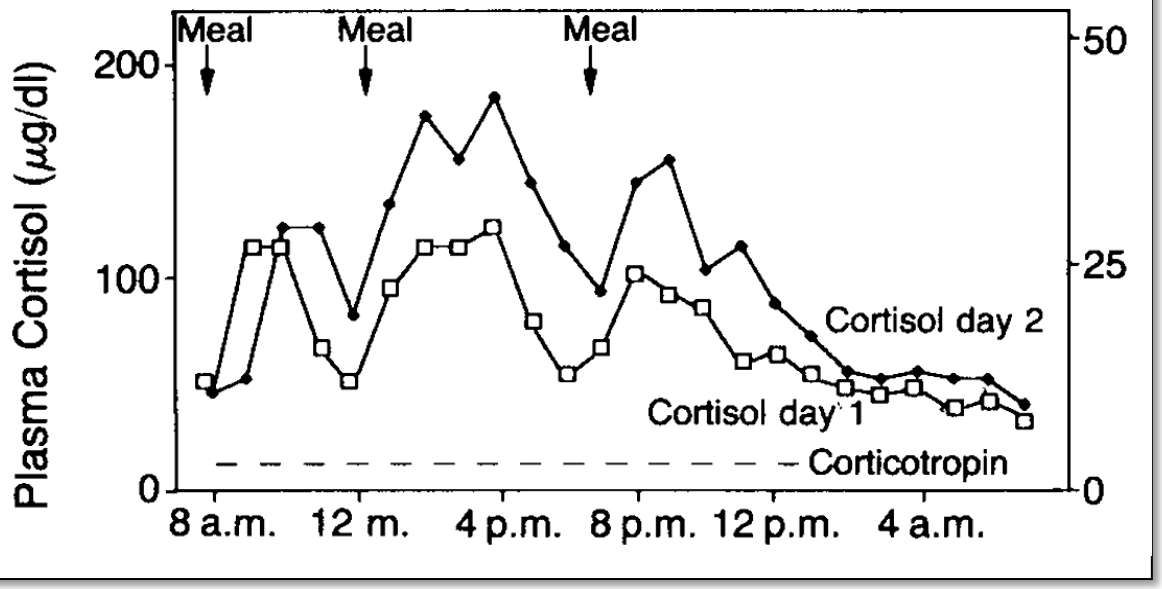


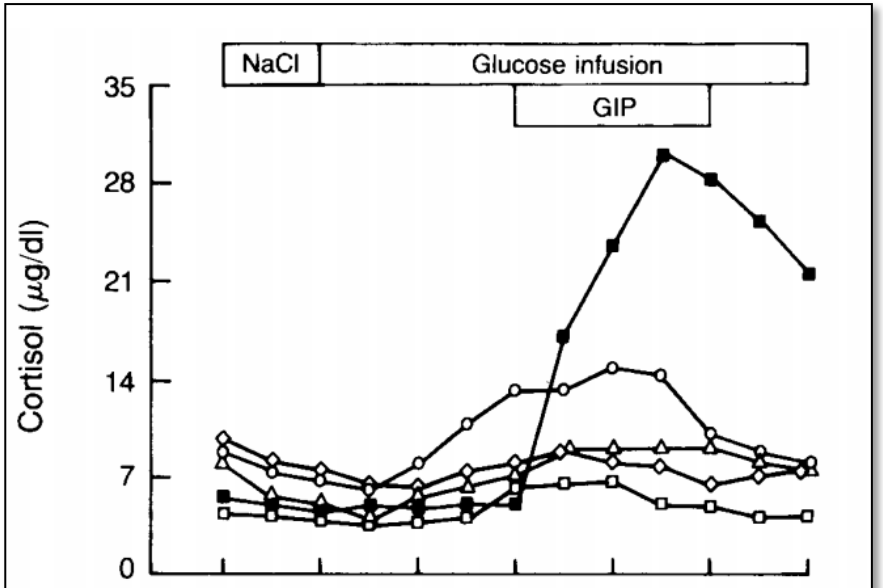
cAMP/PKA pathway activation



FOOD-DEPENDENT CUSHING'S SYNDROME MEDIATED BY ABERRANT ADRENAL SENSITIVITY TO GASTRIC INHIBITORY POLYPEPTIDE

Yves Reznik, M.D., Veronique Allali-Zerah, M.D., Jean A. Chayvialle, M.D., Robert Leroyer, Ph.D., Pierre Leymarie, M.D., Georges Travert, Ph.D., Marie-Christine Lebrethon, M.D., Ilse Budi, M.D., Anne-Marie Balliere, M.D., and Jacques Mahoudeau, M.D.





GASTRIC INHIBITORY POLYPEPTIDE–DEPENDENT CORTISOL HYPERSECRETION — A NEW CAUSE OF CUSHING'S SYNDROME

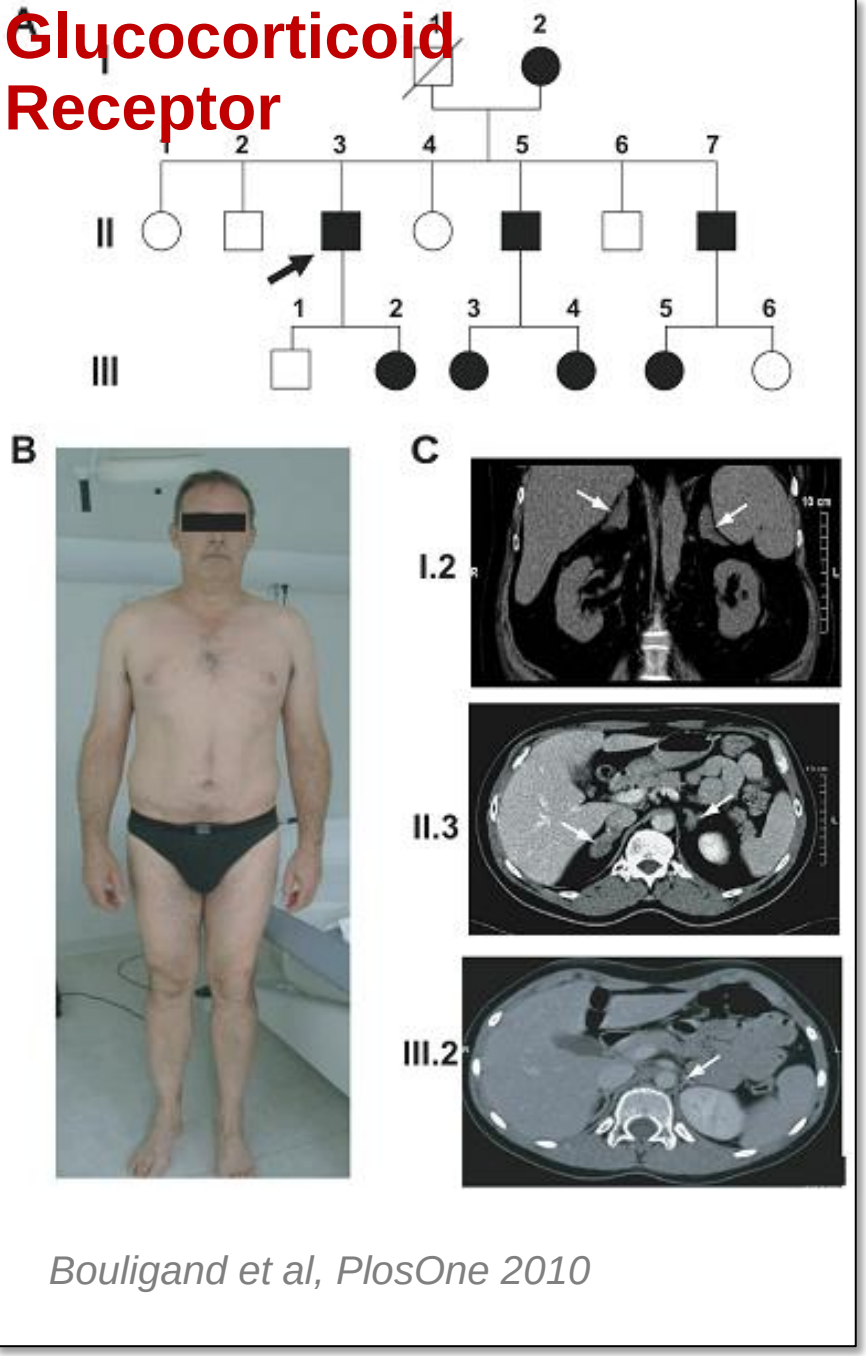
André Lacroix, M.D., Edouard Bolté, M.D., Johanne Tremblay, Ph.D., John Dupré, M.D., Pierre Poitras, M.D., Hélène Fournier, M.D., Jean Garon, M.D., Dominique Garrel, M.D., Francis Bayard, M.D., Ph.D., Raymond Taillefer, M.D., Richard J. Flanagan, Ph.D., and Pavel Hamet, M.D., Ph.D.

List of ectopic receptors

Ligand	*Receptor*	*In vivo response*
GIP	GIPR	Food
Vasopressin	V1a	Postural Test
Epinephrin	ADRB	Postural Test
LH	LH/HCG R	Pregnancy, menopausis
Serotonin	HTR4	Metoclopramide

Duplication of GIPR
LeCoq et al, JCI Insight 2017

Glucocorticoid Receptor



Bouligand et al, PlosOne 2010

APC (Familial Adenomatous Polyposis)

Hsiao et al, 2009
Ymakita et al, 1997
Marchesa et al, 1997

MEN 1 (Multiple Endocrine Neoplasia Type 1)

Skogseid et al, 1992
Burgess et al, 1996
Hsiao et al, 2009

« Common » PMAH?
A genetic disease?

- Bilateral affection

- Rares familial reports

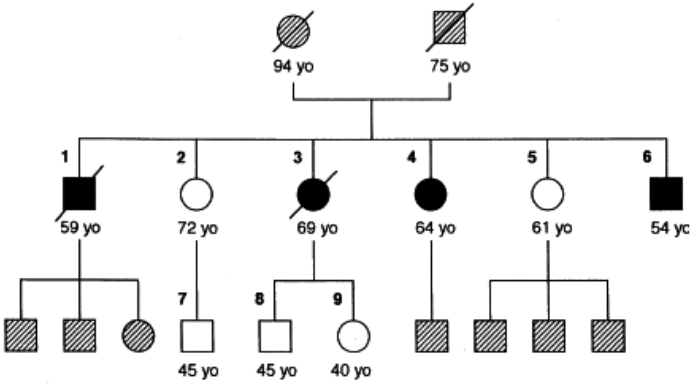
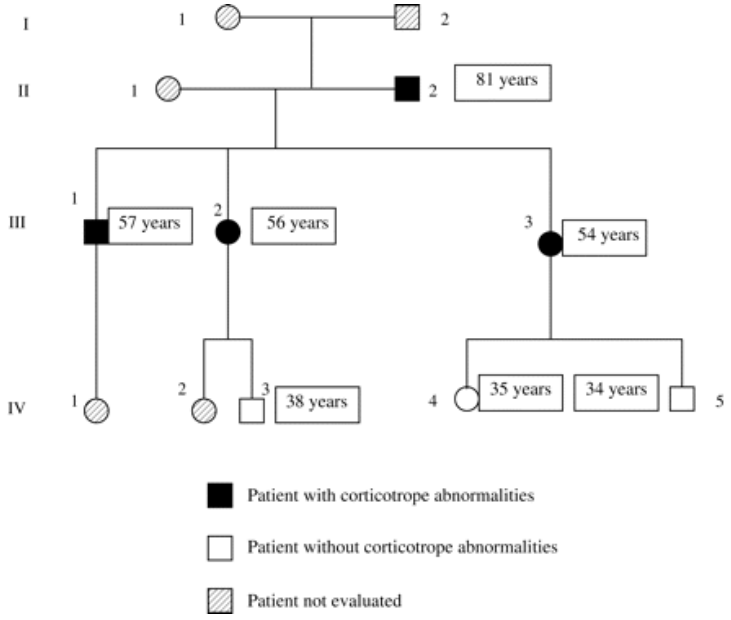


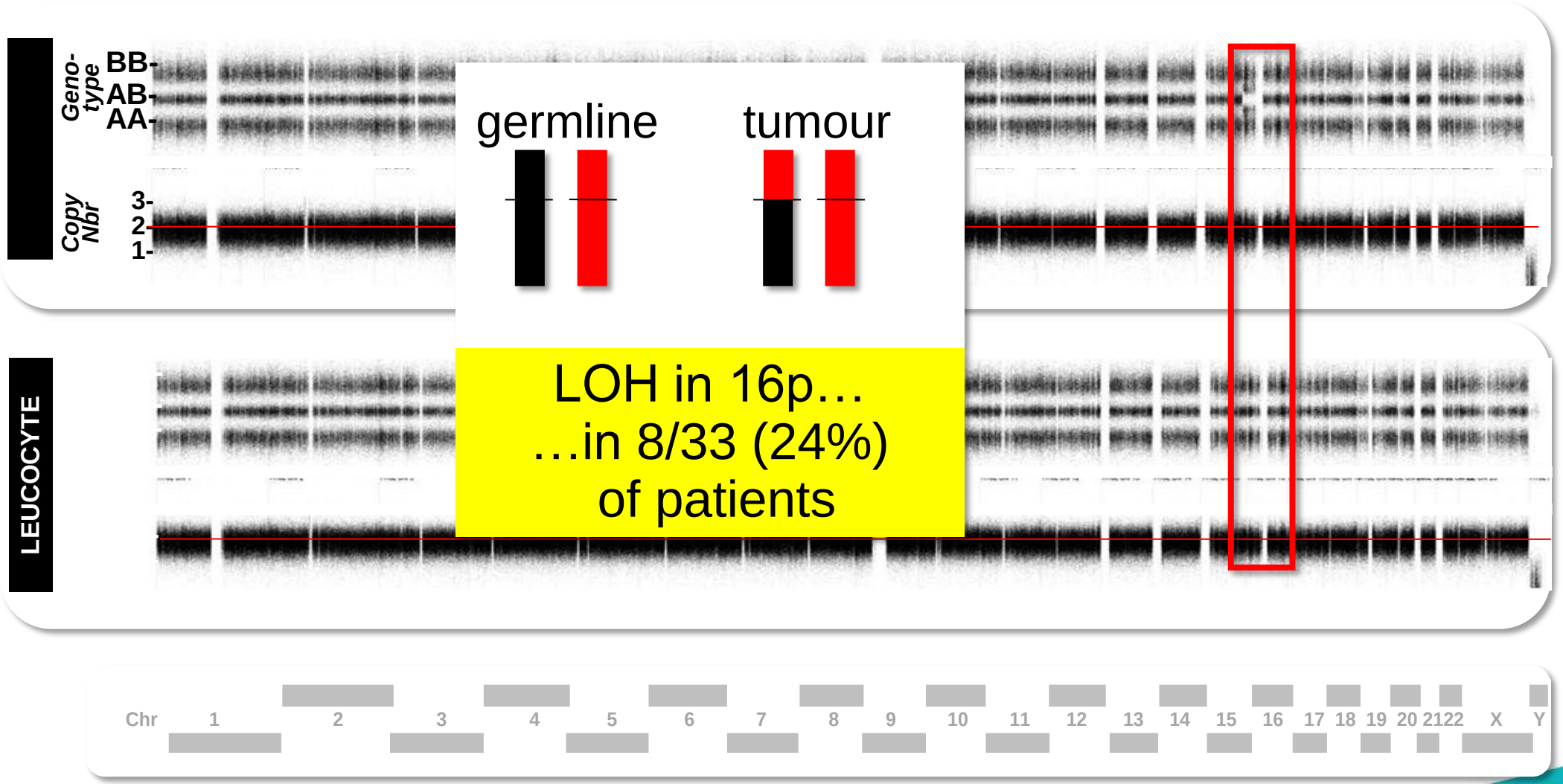
Fig. 1 Pedigree of the family. □, ▨, ■, Male family members; and ○, ◍, ●, female family members. ■, ●, Affected members; □, ○, unaffected members; ▨, ◍, not examined; /, deceased members. The examined members are numbered.

Nies et al. 1996



Vezzosi et al, EJE 2007

SNP Tumor Profiles in PMAH

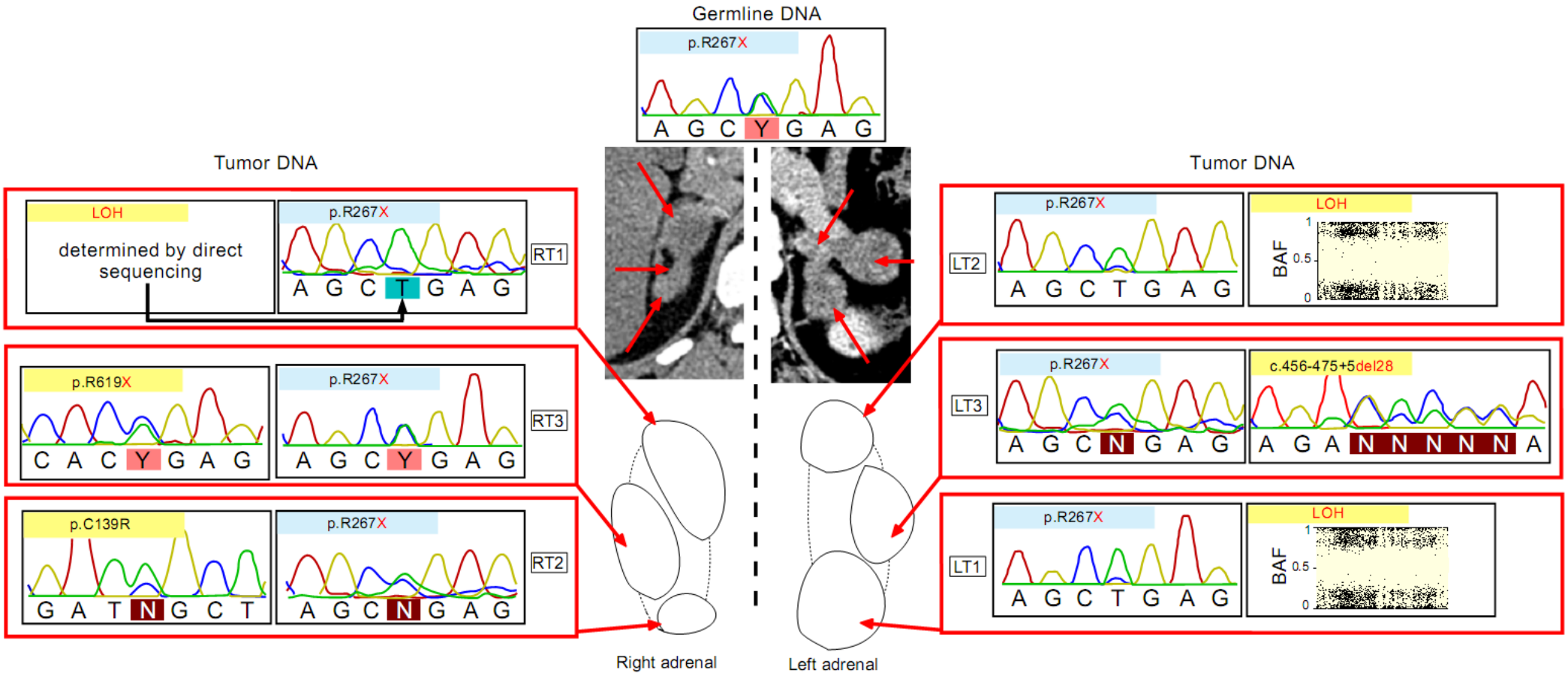


LOH in 16p…
…in 8/33 (24%)
of patients

Assié et al, NEJM 2013

FIRENDO

ARMC5: a tumor suppressor gene



2 hits on *ARMC5*:
-One germline
-One nodule-specific

Correlation genotype-phenotype

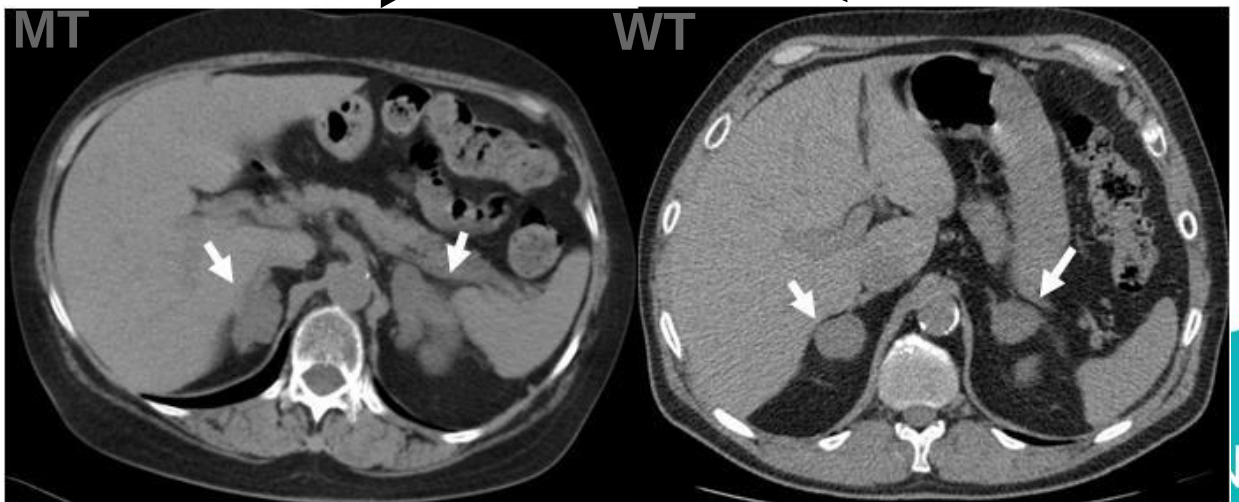

Rossella Libé


Stéphanie Espiard

Characteristics	Mutated (n=24) mean [95%CI]	Wild-type (n=68) mean [95%CI]	P-value
Surgery	20Y/4N	23Y/45N	<0,001
Cortisol after Dexamethasone suppression (µg/dl)	18 [0-38]	6 [0-19,7]	<0.001
Total weight (gr)	107 [28-186]	50 [0-128]	0.001
Number of nodules **2** **3** **4** **5 or more**	 3 1 1 14	 42 9 3 7	<0,001

→ Better classification?

Espiard et al, JCEM 2015
Gagliardi et al, JCEM 2014
Alencar et al, JCEM 2014
Faucz et al, JCEM 2014



Prevalance of ARMC5 mutations in PMAH

- 50% Operated

Assié et al, NEJM 2013

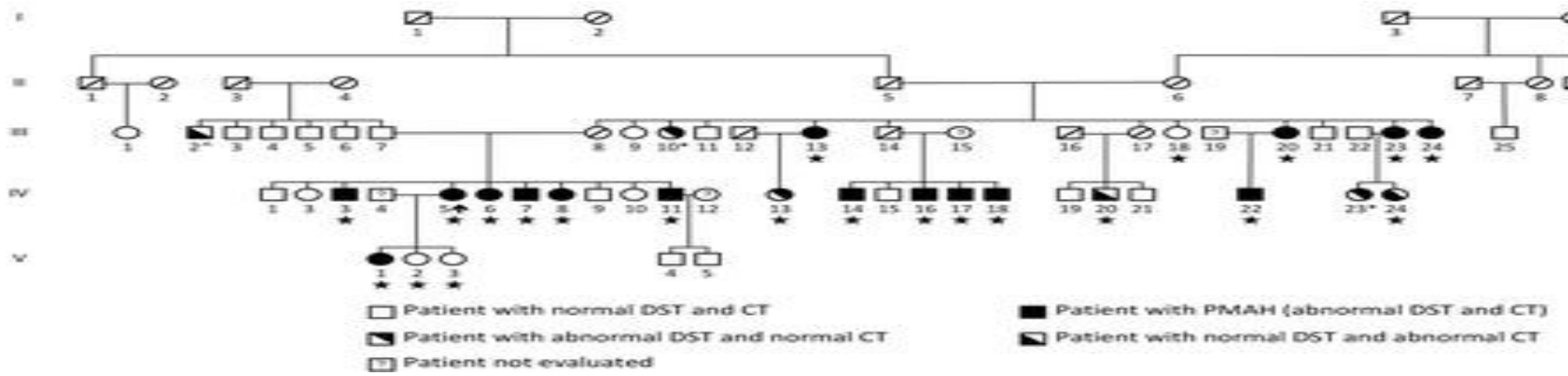
- 25% “Overt” PBMAH

Albiger et al, Endocrine 2017
Espiard et al, JCEM 2015
Gagliardi et al, JCEM 2014
Alencar et al, JCEM 2014
Faucz et al, JCEM 2014

- <5% Bilateral Incidentalomas

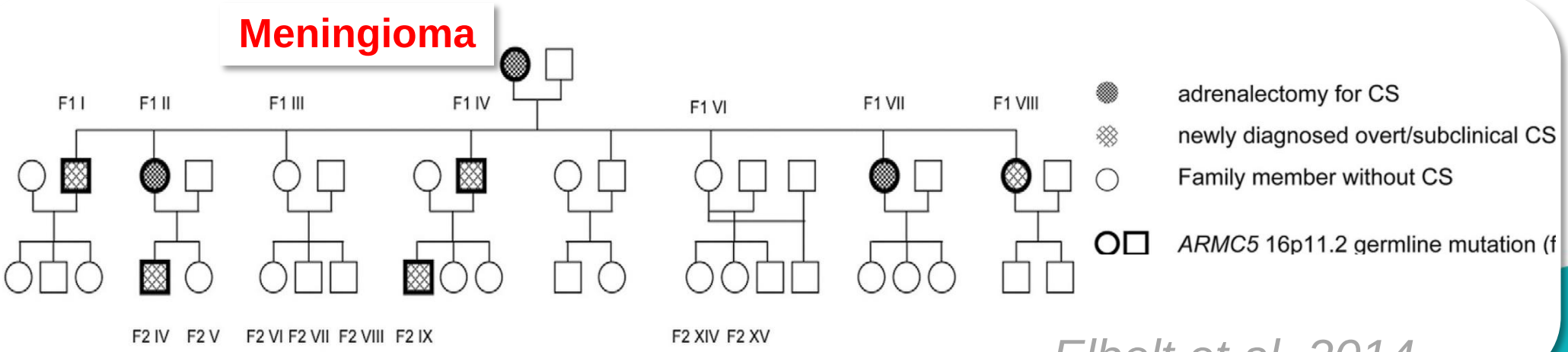
Ems et al, Endocrine 2016

ARMC5-related PMAH is not sporadic, but familial…



Alencar et al, JCEM 2014

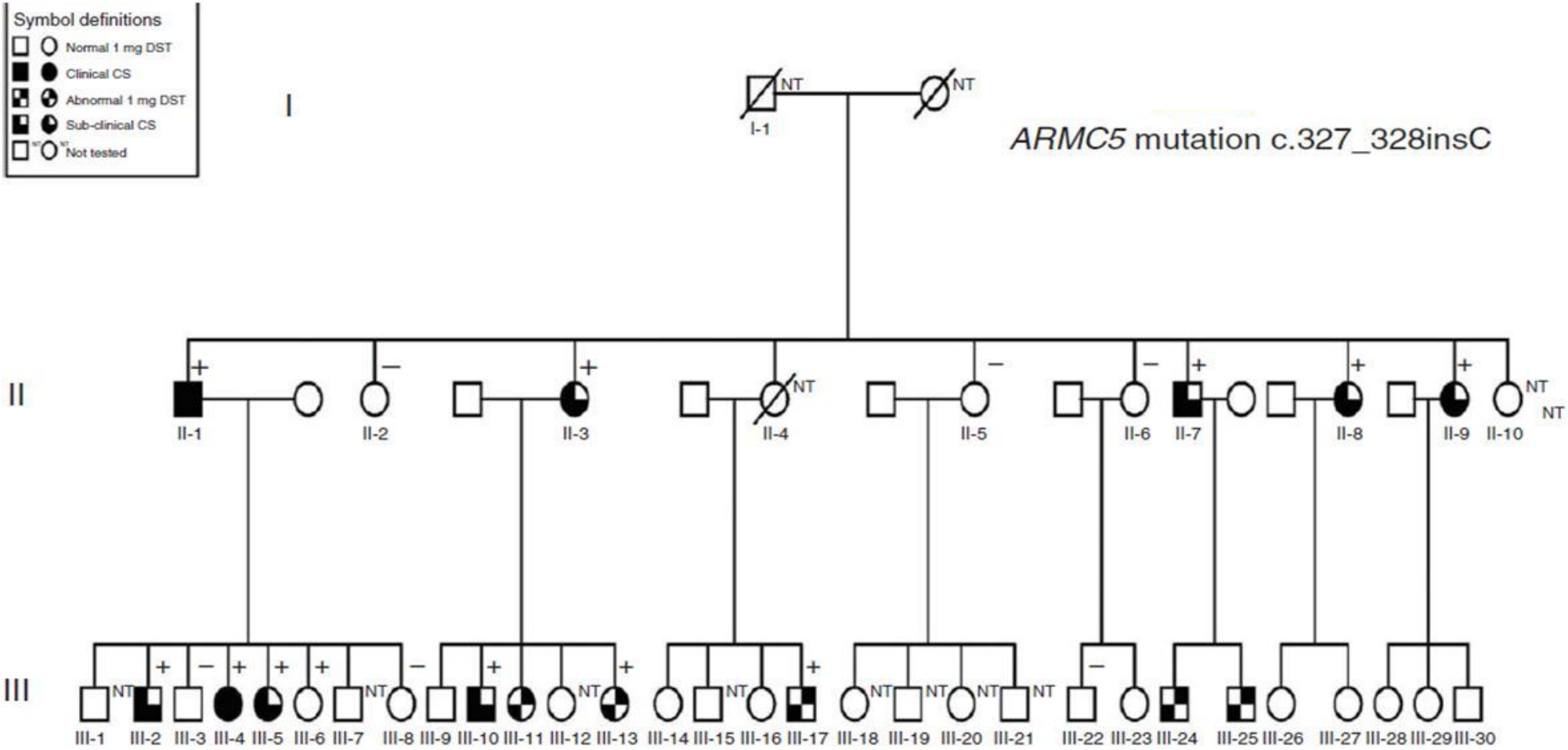
… and potentially syndromic



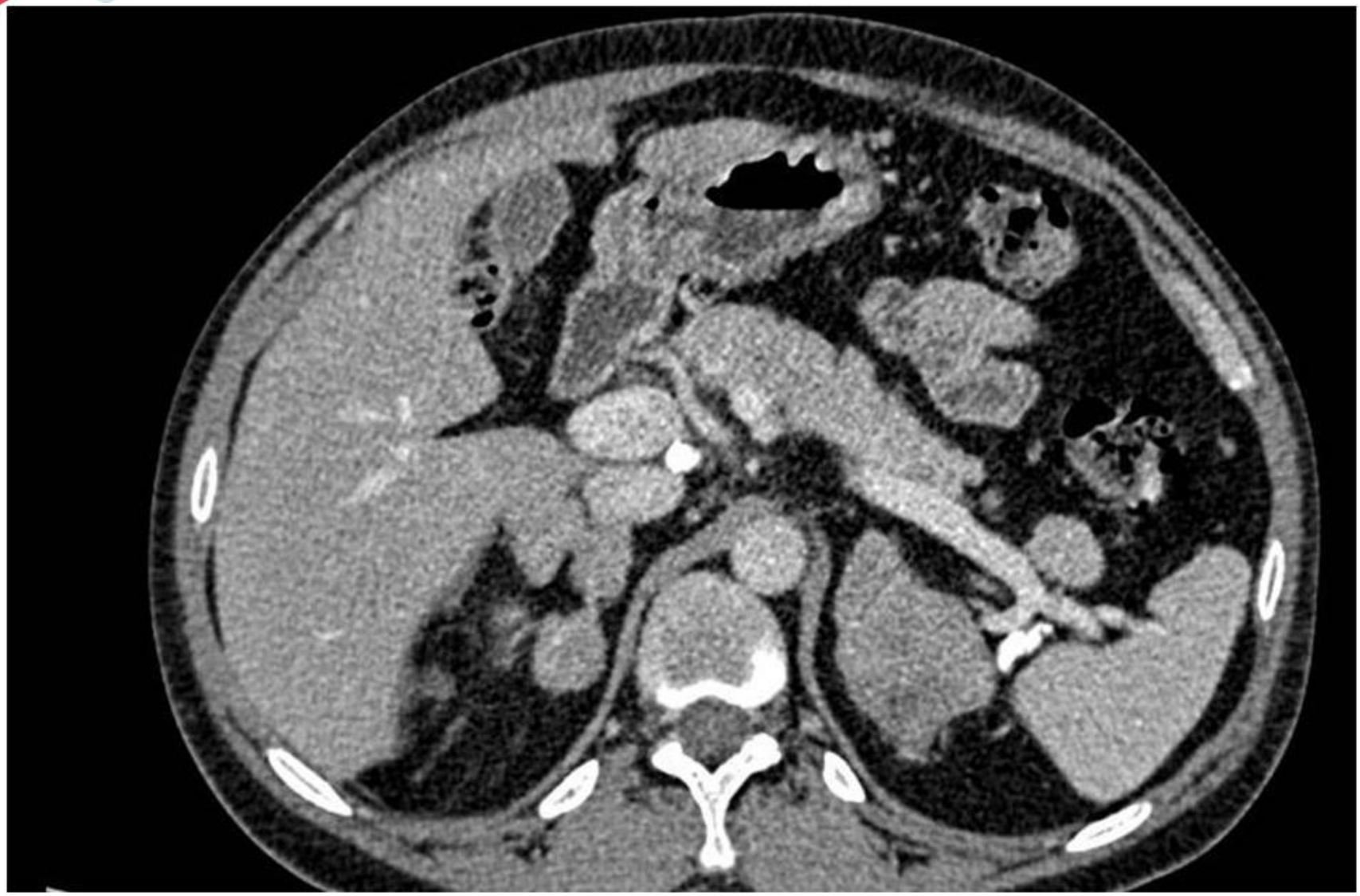
Elbelt et al, 2014

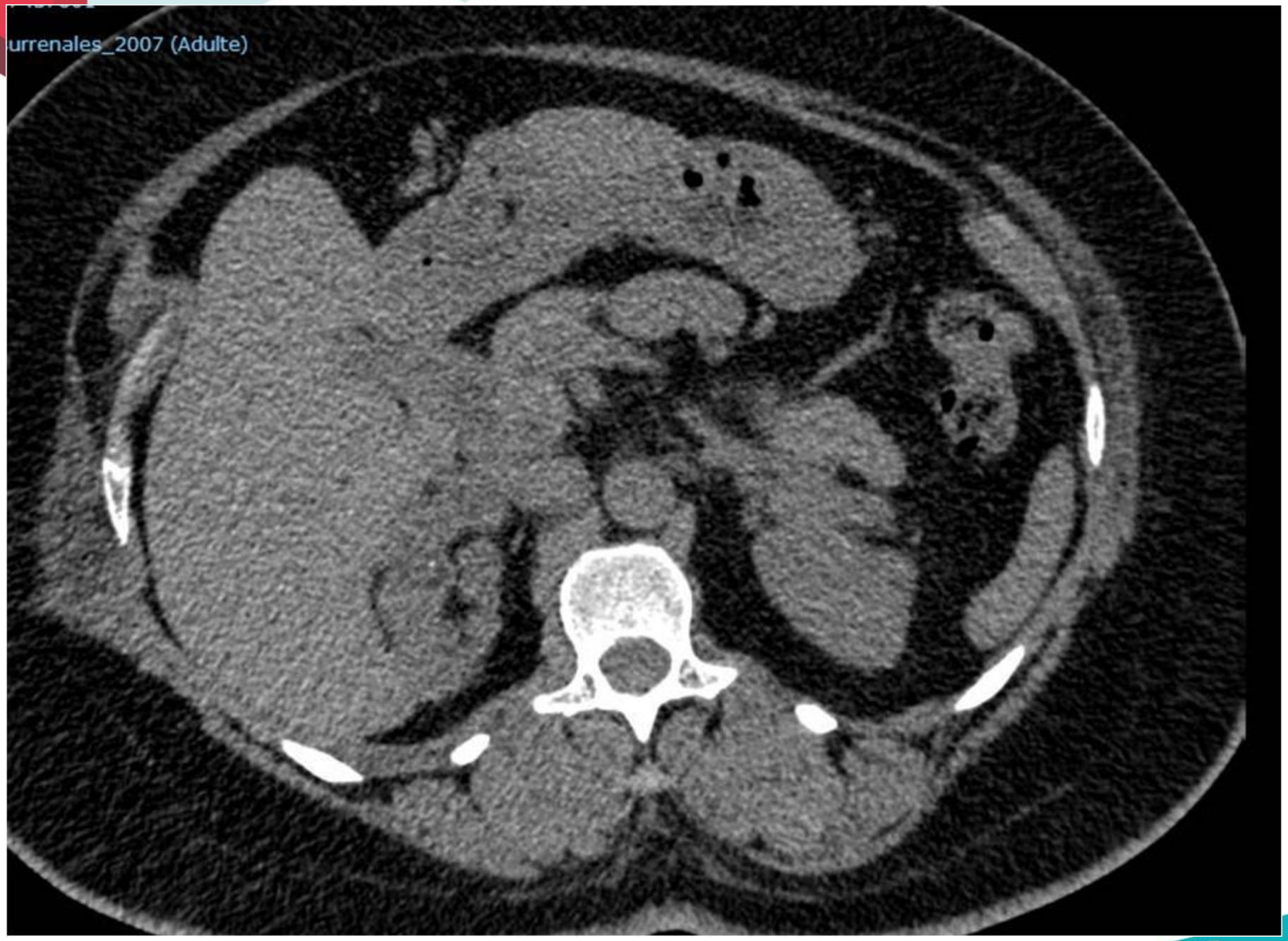
ARMC5-related PMAH is not sporadic, but familial…

Aberrant β-adrenergic and vasopressin response



Bourdeau et al, EJE 2016




urrenales_2007 (Adulte)

Adrenal hyperplasia / dysplasia gene hunt: What are we looking for?

Different sources of DNA

-Somatic « mutations » (tumor suppressors only)

-Germline « mutations » in families

-Germline « mutations » in index cases

Different types of « mutations »

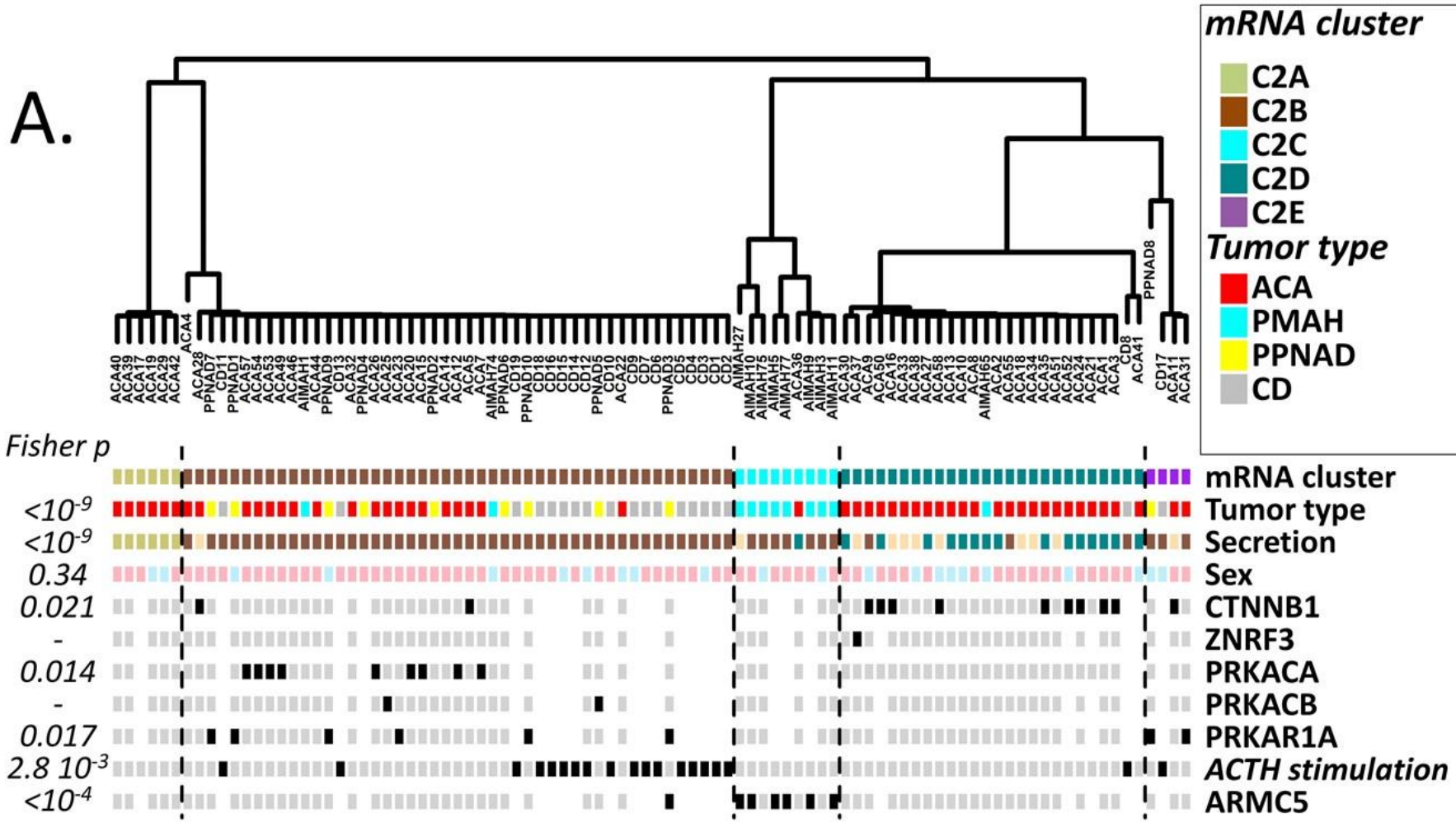
-DNA sequence variations *exome, WGS*

-DNA copy number variations *SNP arrays*

-Chromosome rearrangements neutral for CN and allelic ratios (inversion, translocations, mobile elements insertions) *WGS? Long range seq?*

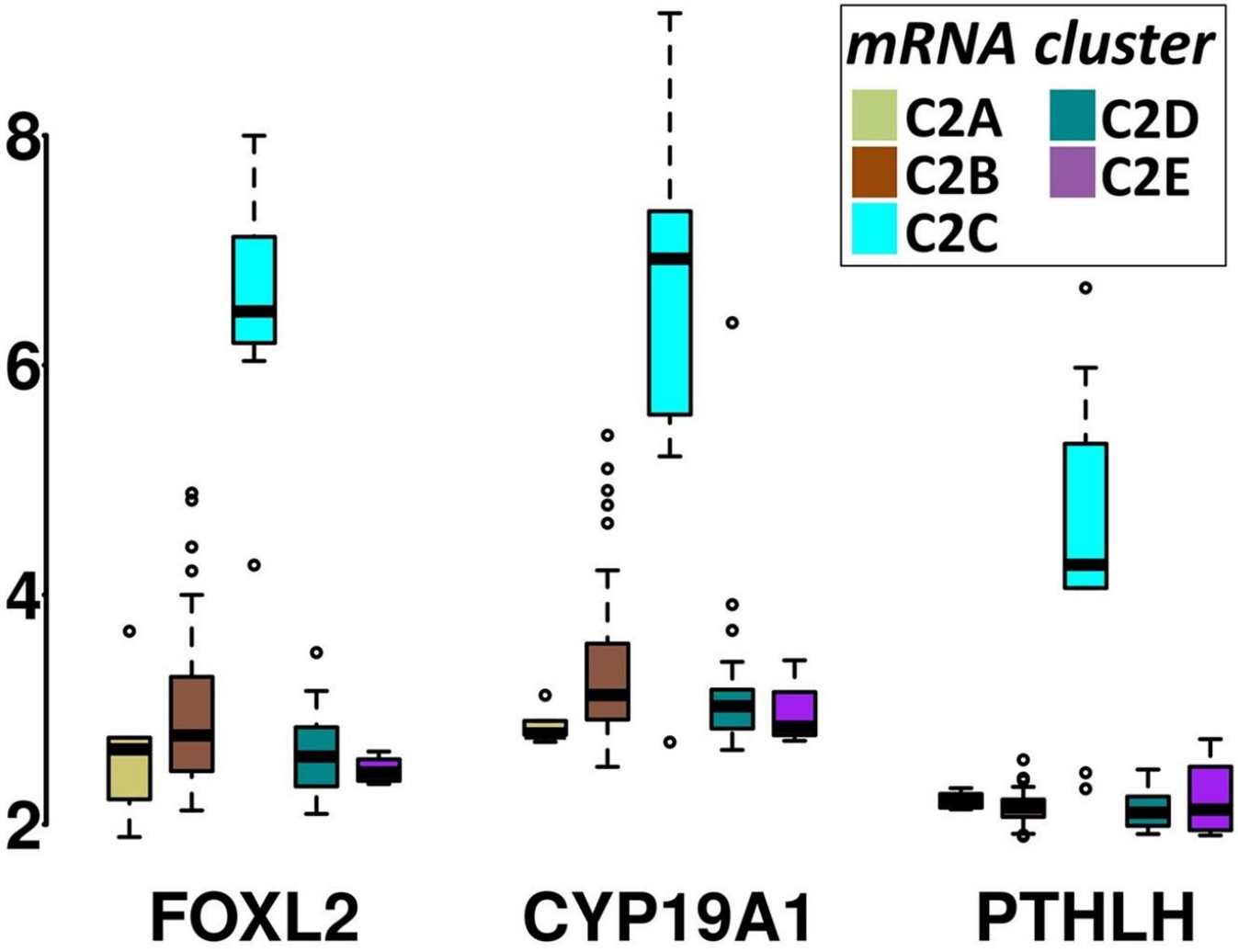
-Epimutations *WGS?*

Transcriptome
4 main subtypes of benign tumors



Faillot et al, unpublished

ARMC5-mutated PMAH
A gonadal signature



Genes expressed in ovaries

Faillot et al, unpublished

Thank you !

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COMETE
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Eric Baudin
Anne Paule Gimenez-Roqueplo
Antoine Tabarin
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Laurence Amar

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Xavier Bertagna
Laurence Guignat
Olivia Barreau
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Najiba Lalhou
Jean Guibourdenche
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Bertrand Dousset
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Mario Néou
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Bruno Ragazzon
Marthe Rizk
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Julien Sakat
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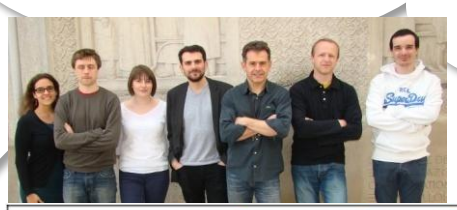
Genomics Cochin Institut
Franck Letourneur team



Bioinformatics CIT
Aurélien de Reyniès
Eric Letouzé

GENOM'IC

CIT Cartes d'identité des Tumeurs

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