Interhospital Conference

SIENDO
Faculty of Medicine Siriraj Hospital

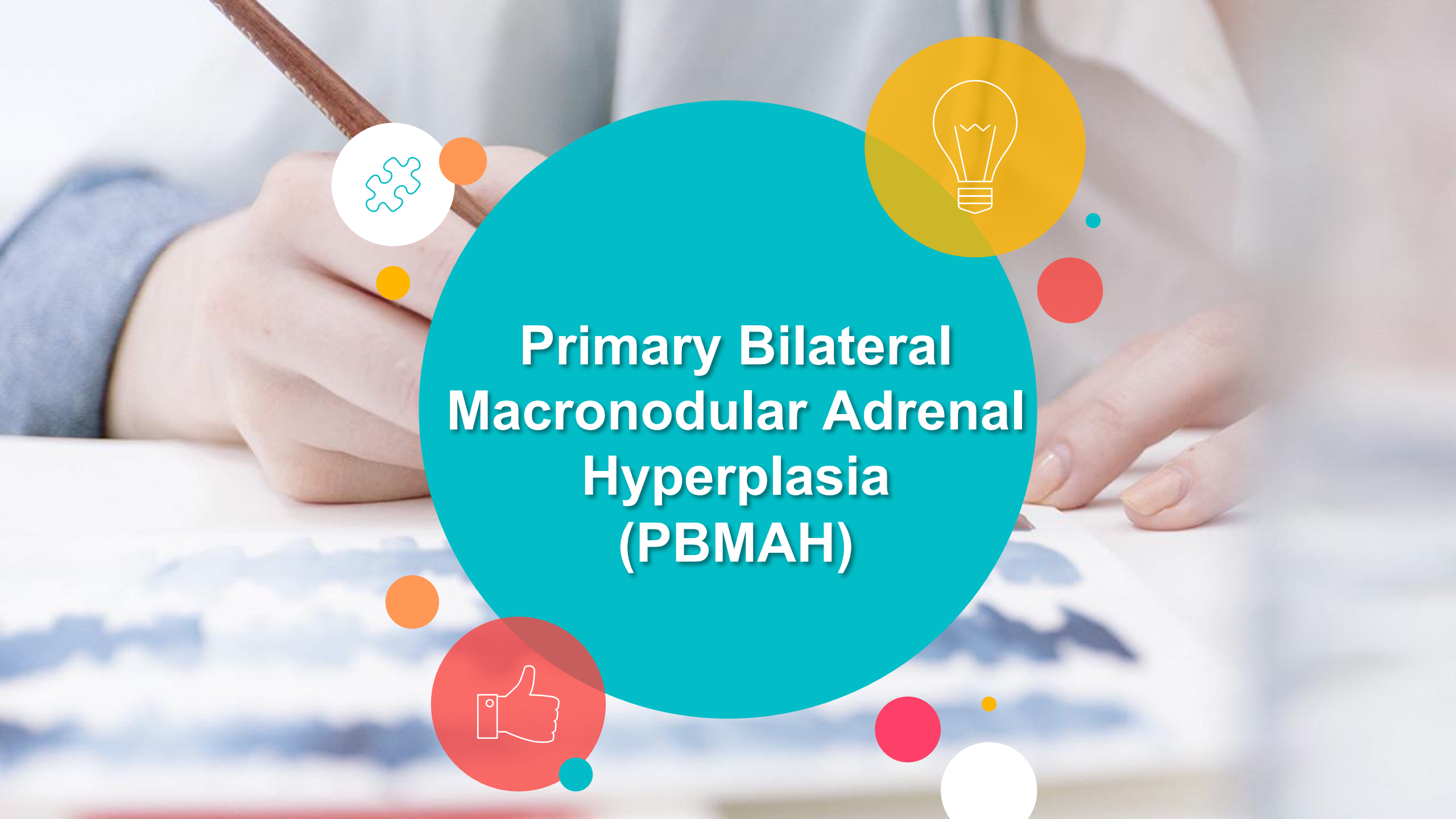
Case 1

Division of Endocrinology and Metabolism

Department of Internal medicine

Siriraj Hospital

December 24th, 2021



Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH)

Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH)

- Macronodular adrenal hyperplasia (MAH): adrenal enlargement by large (>1 cm) nodules
- MAH is a heterogeneous entity presenting in a variety of clinical settings
  - **ACTH-dependent MAH:** Chronic ACTH secretion by tumor (Cushing's disease or ectopic ACTH secretion) or compensation for enzymatic defects of cortisol synthesis (Congenital adrenal hyperplasia)
  - **ACTH-independent MAH** (placed by term PBMAH): Cortisol secretion by steroidogenic cells of the hyperplastic adrenal nodule

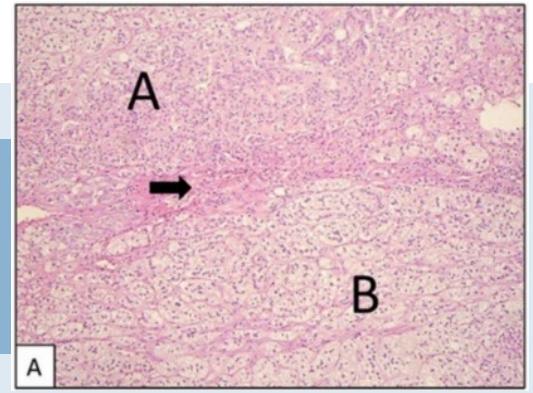
Endocrine-Related Cancer (2019) 26, R567–R581
Dimitra A Vassiliadi and Stylianos Tsagarakis. Diagnosis and management of primary bilateral macronodular adrenal hyperplasia. Endocrine-related cancer. R 567- R 581567

Clinical Presentation

- Majority cases have a sporadic presentation with a female preponderance, but also familial cases encountered with an equal female-to-male ratio
- Between the ages of 40 and 60 years
- High clinical heterogeneity: severe form (overt CS) to asymptomatic form
  - Majority of PBMAH cases present with mild clinical picture remaining undiagnosed until abdominal imaging for an unrelated reason reveals bilateral adrenal enlargement (Incidentaloma)
  - Minority of PBMAH cases present with clinically overt CS or detect (only < 2%) during evaluation of clinical hypercortisolism

Endocrine-Related Cancer (2019) 26, R567–R581

Pathology



- Adrenal macronodules define as more than 1 cm, strikingly large, weighing more than 10–100 times the normal weight
- Multiple macronodules can be seen in each adrenal gland and adrenal diameter may reach 10–12 cm

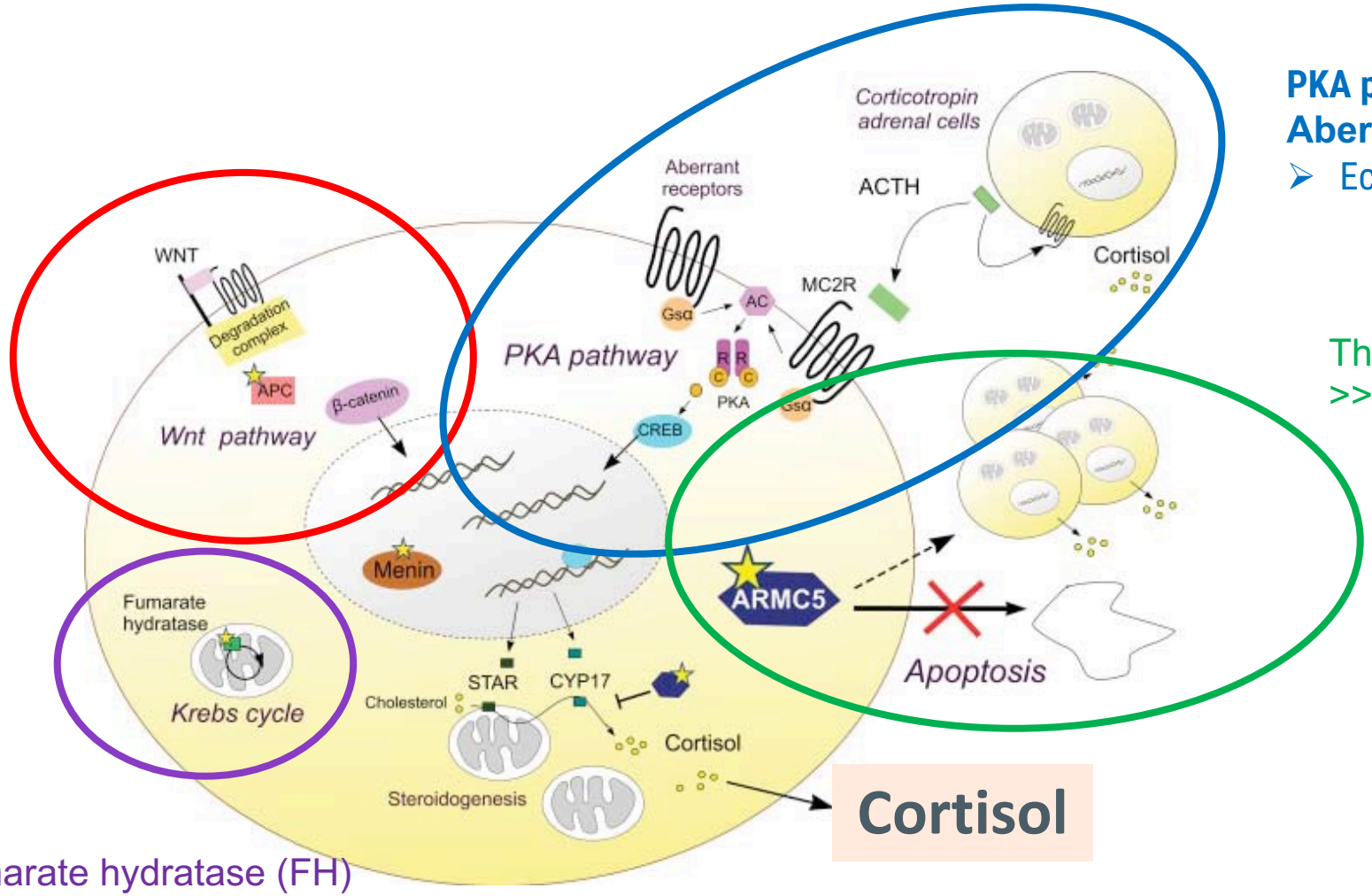
- Two histologic subtypes
  - PBMAH with atrophic inter-nodular cortex (type 1)
  - PBMAH with both nodular and inter-nodular tissue hyperplasia (type 2)
- The nodules usually consist of two types of cells
  - Large clear cells (spongiocytes): positive IHC for 3-beta-HSD
  - Smaller compact cells: positive IHC for 17-hydroxylase

Endocrine-Related Cancer (2019) 26, R567–R581

Pathophysiology

Wnt pathway

- Mutation of APC
- ↑ b-catenin in the cytoplasm and nucleus
- Stimulates target gene expression such as WISP2, GSK3B, and CTNNB1
- Adrenal growth



PKA pathway
Aberrrant hormone receptors

- Ectopic or eutopic receptor

The mutations of **ARMC5**
>> ↓ Apoptosis of AC cells

Cortisol

Krebs cycle

- Mutations of fumarate hydratase (FH)

European Journal of Endocrinology (2015) 173, M121–M131

Pathophysiology: PKA pathway

1. Aberrantly expressed G-protein-coupled receptors (GPCRs) by ligands other than ACTH (77-87%)

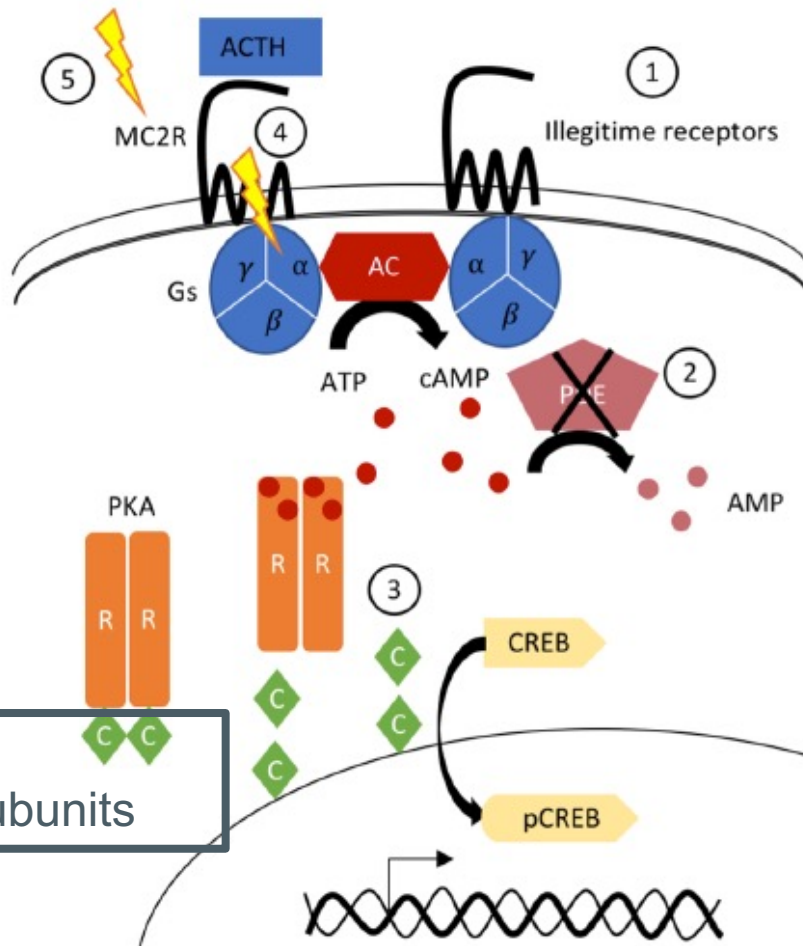
2. Decreased activity of phosphodiesterase (PDE) – PDE11A and PDE8B defect (micronodular hyperplasia)

3. Duplication of the catalytic subunit (PRKACA)

4. Activating mutations of MC2R (adrenal growth)

5. Activating mutations of GNAS (adrenal nodule formation)

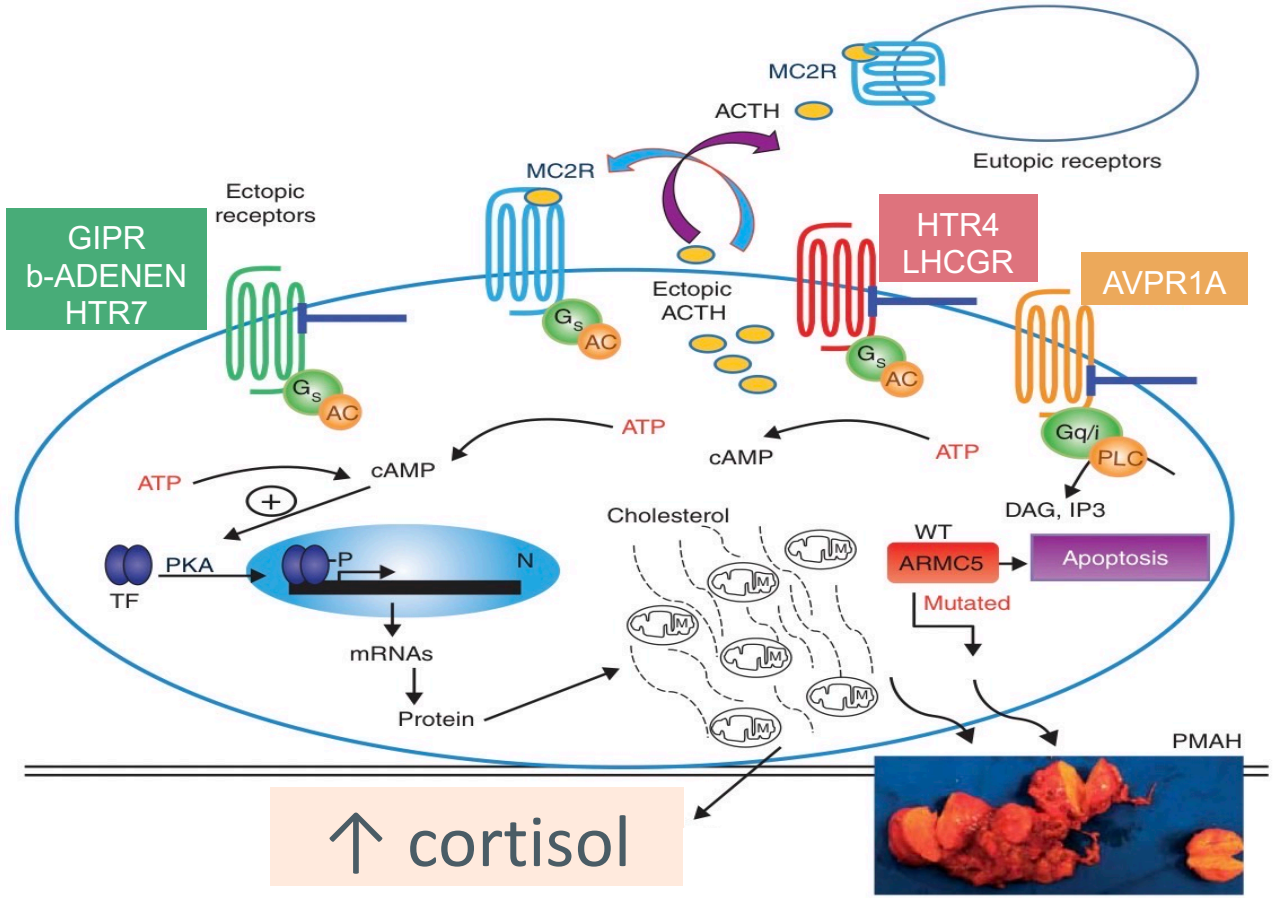
6. ↓ Hydrolysis of cAMP
↑ Expression and activity of PKA subunits



Genetic alteration

Endocrine-Related Cancer (2019) 26, R567–R581
Endocrine-Related Cancer (2018) 25, R131–R152

Pathophysiology: Aberrant hormone receptors



- 77–87% of patients with PBMAH
- 50% of the patients indicating that multiple aberrant receptors may co-exist in each patient
- Ectopic receptor: GIP, catecholamine, V2 or V3, serotonin and AT1 receptors
- Eutopic receptor (overexpress): V1, LH/hCG, serotonin and leptin receptor

Endocrine-Related Cancer (2019) 26, R567–R581
Journal of Endocrinology (2015) 224, R31-R43

Genetics

Table 1 Genes identified in PBMAH.

Gene	Locus	Function of the WT protein	Associated manifestations
ARMC5	16p11	No known function, potential role in regulation of apoptosis and steroidogenesis	Meningioma?
Menin	11q13	Regulator of gene transcription, cell proliferation, apoptosis, and genome stability	Multiple endocrine neoplasia type 1 (MEN1): hyperparathyroidism, pituitary adenomas, pancreatic neuroendocrine tumors
FH	1q42	Krebs cycle, amino acid metabolism	Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)
PDE11A	2q31-35	Hydrolysis of cAMP and cGMP	Isolated
GNAS1	20q13	Stimulation of adenyl cyclase, activation of the cAMP/PKA pathway	McCune Albright syndrome: fibrous bone dysplasia, café-au-lait spots, precocious puberty, acromegaly, toxic multinodular goiter
APC	5q12-22	Prevent β-catenin accumulation, inhibition of the Wnt/β-catenin pathway	Familial adenomatous polyposis: colon adenomas and carcinomas, pigmented retinal lesions, desmoids tumors, other malignant tumors as adrenocortical carcinomas
MC2R	18p11	ACTH receptor, activation of the cAMP/PKA pathway	Isolated
PRKACA	19p13.1	Catalytic subunit of PKA, activation of the cAMP/PKA pathway	

European Journal of Endocrinology (2015) 173, M121–M131

Genetics

Table 1 Frequency of patients with ARMC5 mutations among apparently sporadic cases of PBMAH.

	ARMC5 mutated patients with overt CS % (n/total)	ARMC5 mutated patients with 'subclinical' CS % (n/total)	ARMC5 mutated patients without cortisol hypersecretion
Assie *et al*. 2013	58% (15/26)	50% (3/6)	–
Alencar *et al*. 2014	24% (5/21; 4 with overt and 1 with 'subclinical' CS)		–
Faucz *et al*. 2014	33% (7/21)	0	–
Espiard *et al*. 2015	41% (17/41)	16% (7/43)	0/8
Emms *et al*. 2016	–	5% (1/20)	0/19
Albiger *et al*. 2017	28% (9/32)	5% (1/19)	0/18
Yu *et al*. 2018	44% (4/9)	7% (1/14)	–
Overall	40% (52/129)	11% (13/115)	

- It has recently been shown that a fair number of patients carry germline mutations of the *ARMC5* gene
- Two-hit model: same germline mutation, different second somatic alteration
- *ARMC5* mutations
  - Reduce steroid secretory capacity >> impaired steroidogenesis (early)
  - Increase secretion of steroid precursors
  - Increase adrenal mass >> increase cortisol secretion (late)
- *ARMC5* mutations are common in patients with PBMAH
  - They account for the vast majority of familial cases (13/16)
  - The frequency of sporadic cases are varies: 40% (28–55%) in overt CS patients, 11% in subclinical CS patients

Indolent and slow progression

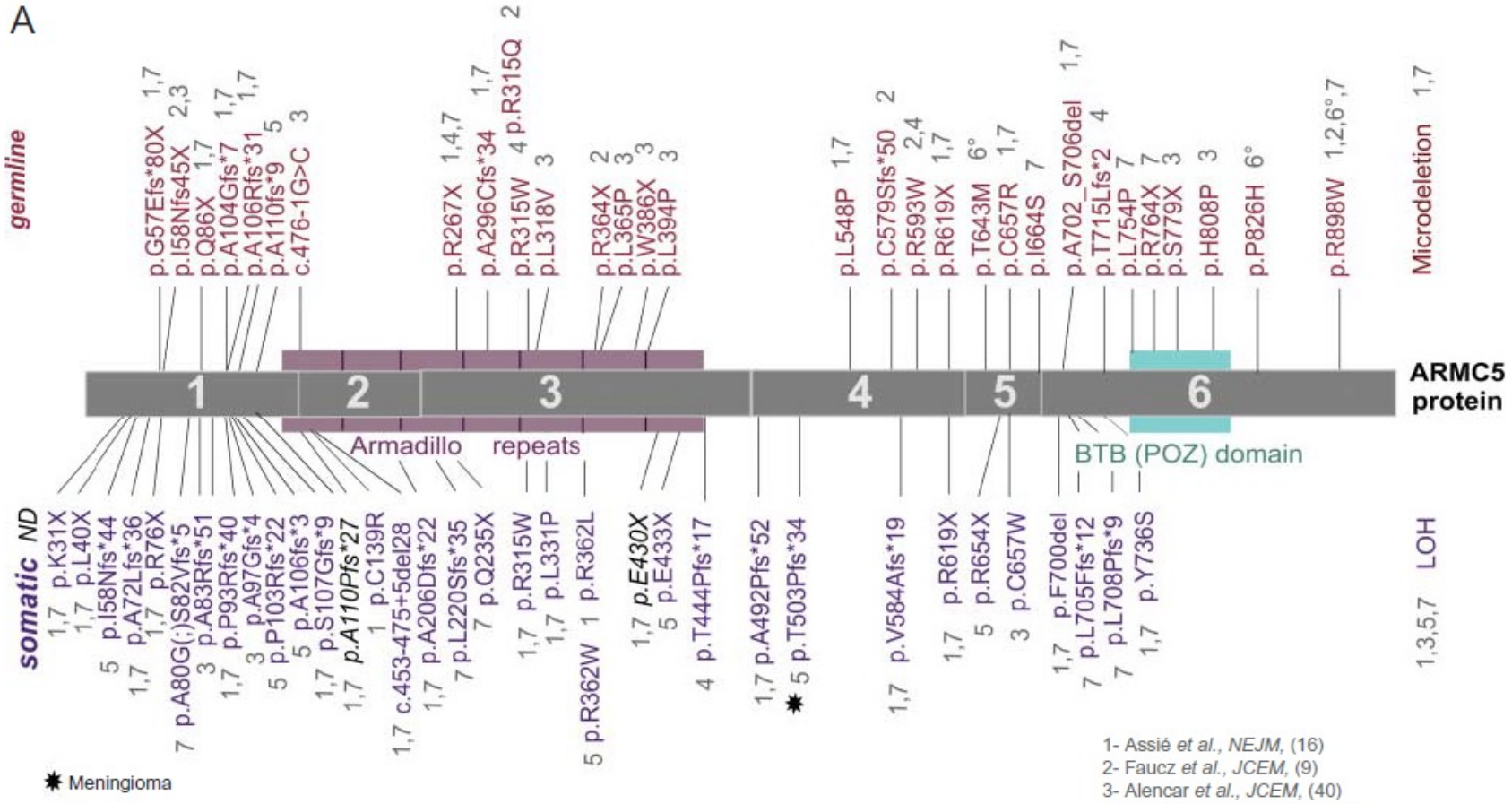
Endocrine-Related Cancer (2019) 26, R567–R581

ARMC5 mutation

- Armadillo repeat containing 5 (Tumor suppressor gene: main genetic cause of PBMAH)
- Located at chromosome 16p11.2
- Associated with a more severe disease (higher cortisol levels, larger adrenal glands and higher numbers of nodules)
- 29 germline mutations, 32 somatic mutations, non-determinate[1]
  - Two studies described occurrence of meningiomas in several ARMC5-mutated patients
  - The ARMC5 gene will be a causal gene in both PBMAH and meningioma?
- Assessed Whole genome sequencing for the occurrence of further neoplasias in PMAH affected family (17 participants)[2]
  - 2/17 participant: intracranial meningioma (11 episodes, 1 episode)
  - Patho: WHO grade I, meningothelial subtype
  - Germline mutation with somatic mutation of ARMC5 gene (second hit)

European Journal of Endocrinology (2015) 173, M121–M131[1]
J Clin Endocrinol Metab, January 2015, 100(1):E119–E128 [2]

ARMC5 mutation



29 germline mutations (written in red)

32 somatic mutations (written in purple)

2 non-determinate (written in black italic, ND)

* indicates mutations identified in meningioma

European Journal of Endocrinology (2015) 173, M121–M131

Diagnostic evaluations

Depend on clinical context (heterogeneity)

- **Imaging characterization**
  - Massively enlarged adrenals with multiple macronodules distorting the normal adrenal configuration
  - CT scan, MRI, FDG-PET/CT scan
- **Endocrine evaluation (incidentaloma)**
  - All patients; pheochromocytoma, **ACS**
  - HT patients; primary aldosteronism
- **Evaluation of genetically predisposed individuals *****

- **1 mg overnight DST**: cortisol level (mcg/dL)
  - ≤ 1.8 exclude ACS
  - 1.9 - 5.0 possible ACS
  - > 5 confirm ACS
- **Midnight cortisol or 24 hr UFC**: degree of cortisol excess
- **ACTH level, DHEA-s level**

PBMAH: ↑ steroid precursors: DHEA
↑ midnight salivary or serum cortisol
Lack of cortisol post-DST

Endocrine-Related Cancer (2019) 26, R567–R581

Diagnostic evaluations

- Evaluation of genetically predisposed individuals ***
  - After the discovery that a significant percentage of apparently sporadic cases are due to ARMC5 mutations, family history is not a reliable indicator
  - Clinical, biochemical or imaging criteria may be more relevant
  - Patients with cortisol excess and large multinodular adrenal glands may be more likely to harbor an ARMC5 mutation, but this needs to be proven
  - Genetic screening of family members of ARMC5-mutated patients resulted in recognition of asymptomatic or pre-symptomatic cases
  - PBMAH may present with incomplete or delayed penetrance

Endocrine-Related Cancer (2019) 26, R567–R581

Treatment - Surgical treatment

- Bilateral adrenalectomy
  - Treatment of choice for patients with overt CS due to PBMAH
  - Post-adrenalectomy lifelong adrenocortical hormone replacement and increase risk of adrenal crisis
- Unilateral adrenalectomy
  - Patient with moderately increased cortisol level but with clinical of cortisol excess
  - Lower complications compared to bilateral adrenalectomy
  - Consider adrenal venous sampling (lateralization often coincides with the largest adrenal)
  - 1/3 had transient adrenal insufficiency
  - Recurrent rate 10-15% in 15 years (indolent and slowly progression)

Endocrine-Related Cancer (2019) 26, R567–R581

Treatment – Medication

- Adrenal enzyme inhibitors: to control cortisol secretion before surgery
- In case of aberrant receptors have been identified
  - Targeted treatment blocking aberrant receptors have been effective as alternatives to adrenalectomy

Aberrant receptor expression	Treatment option
Gastric inhibitory polypeptide (GIP)	Somatostatin analog (octreotide, pasireotide)
Catecholamine	Beta-adrenergic receptor antagonist (propanolol)
LH/hCG	Long-acting GnRH agonist (leuprolide acetate)
Angiotensin II type 1 (AT-1)	AT-1 antagonists

Endocrine-Related Cancer (2019) 26, R567–R581

Thank you