

From the First Case Reports to *KDM1A* Identification: 35 Years of Food (GIP)-Dependent Cushing's Syndrome

Authors

Lucas Bouys^{1,2}, Jérôme Bertherat^{1,2}

Affiliations

- 1 Department of Endocrinology and National Reference Center for Rare Adrenal Diseases, Hôpital Cochin, Assistance Publique Hôpitaux de Paris, 27 rue du Faubourg Saint-Jacques, F-75014, Paris, France
- 2 Genomics and Signaling of Endocrine Tumors, Institut Cochin, INSERM U1016, CNRS UMR 8104, Université Paris-Cité

Keywords

PBMAH, adrenal, cushing's syndrome, food-dependent, GIP-dependent, GIP, GIPR, *KDM1A*

received 12.02.2024

revised 14.06.2024

accepted 27.06.2024

published online 26.07.2024

Bibliography

Exp Clin Endocrinol Diabetes 2024; 132: 697–704

DOI 10.1055/a-2359-8051

ISSN 0947-7349

© 2024, Thieme. All rights reserved.

Georg Thieme Verlag KG, Oswald-Hesse-Straße 50, 70469 Stuttgart, Germany

Correspondence

Prof Jérôme Bertherat

Department of Endocrinology and National Reference

Center for Rare Adrenal Diseases

Hôpital Cochin, Assistance Publique Hôpitaux de Paris, 27 rue du Faubourg Saint-Jacques

F-75014 Paris

France

Tel: + 33158411895, Fax: + 33146338060

jerome.bertherat@aphp.fr

ABSTRACT

Food-dependent Cushing's syndrome (FDCS) is a rare presentation of hypercortisolism from adrenal origin, mostly observed in primary bilateral macronodular adrenal hyperplasia (PBMAH) but also in some cases of unilateral adrenocortical adenoma. FDCS is mediated by the aberrant expression of glucose-dependent insulinotropic peptide (GIP) receptor (GIPR) in adrenocortical cells. GIP, secreted by duodenal K cells after food intake, binds to its ectopic adrenal receptor, and stimulates cortisol synthesis following meals. FDCS was first described more than 35 years ago, and its genetic cause in PBMAH has been recently elucidated: *KDM1A* inactivation by germline heterozygous pathogenic variants is constantly associated with a loss-of-heterozygosity of the short arm of chromosome 1, containing the *KDM1A* locus. This causes biallelic inactivation of *KDM1A*, resulting in the GIPR overexpression in the adrenal cortex. These new insights allow us to propose the *KDM1A* genetic screening to all PBMAH patients with signs of FDCS (low fasting cortisol that increases after a mixed meal or oral glucose load) and to all first-degree relatives of *KDM1A* variant carriers. Given that *KDM1A* is a tumor suppressor gene that has also been associated with monoclonal gammopathy of uncertain significance and multiple myeloma, the investigation of FDCS in the diagnostic management of patients with PBMAH and further genetic testing and screening for malignancies should be encouraged.

Introduction

Food-dependent cortisol secretion is a rare feature that can be observed in unilateral or bilateral benign adrenal causes of Cushing's syndrome, namely adrenocortical adenomas and primary bilateral macronodular adrenal hyperplasia (PBMAH) [1]. Its first description in 1987 [2] was followed by numerous reports and attempts to understand its origins until the recent discovery of its molecular cause [3, 4]. In this review, we propose both a historical perspective and practical keys for the clinical management of food-dependent (also referred to as "glucose-dependent insulinotropic peptide (GIP)-dependent")

Cushing's syndrome (FDCS). This review article was commissioned after a lecture on this topic at the 2023 IMPROCUSH meeting.

Isolation of glucose-dependent insulinotropic peptide and its receptor

GIP is a 42 amino acid-long protein secreted by the duodenal K cells in response to carbohydrates and fat intake, as well as protein intake, but to a lesser extent. The history of the discovery of GIP is a series of failures and successes and has been brilliantly related by Vincent Marks in a 2020

special issue of peptides dedicated to GIP [5]. In the late 1960s, John C. Brown in Canada first isolated a gastrointestinal polypeptide with the characteristics of an enterogastrone—a hormone secreted by the lower gastrointestinal tract in response to fat intake that inhibits gastric acid secretion and emptying [6]—and then named it gastric inhibitory polypeptide. During the same time, Desmond S. Turner in England was assessing the incretin activity of a supposed polypeptide isolated from a gastrointestinal extract, named insulin releasing peptide (IRP) [7]. A few years earlier, Turner was one of the re-discoverers of the concept of incretin [8, 9]—a gastrointestinal hormone secreted by the small intestine in response to oral carbohydrate intake, stimulating the insulin secretion by the pancreatic beta cells—which had been first described more than 30 years earlier by Laughton and Macallum [10]. The incretin activity of Turner's IRP was poor compared to that of GIP which he obtained from Brown [11, 12]. IRP was then abandoned, and GIP was renamed glucose-dependent insulinotropic polypeptide, as its enterogastrone properties were actually weakly relevant compared to other gastrointestinal peptides. It was demonstrated many years later that Turner's IRP contained both GIP and somatostatin, accounting for its moderate insulinotropic effect [5]. The effects of GIP are actually much wider than only on stomach and beta cells: it also promotes bone formation, fat accumulation, both insulin and glucagon secretion, and beta cell proliferation, among other pleiotropic functions [13]. This explains the current development of drugs targeting the GIP receptor (GIPR) for the treatment of obesity and diabetes.

GIPR was isolated and cloned simultaneously by three independent teams in 1995 [14–16]. The human *GIPR* gene is 13.8 kb long and consists of 14 exons, encoding a 466 amino acids protein, with a homology with rat *Gipr* > 80%. GIPR is a seven-domain transmembrane G-protein-coupled receptor (GPCR) broadly expressed in numerous human tissues. In pancreatic beta cells, where the GIP action is the most documented, GIP is secreted after food intake and binds to its receptor, leading to the recruitment of *G α s* protein and the activation of the cAMP/PKA pathway, finally stimulating insulin secretion [17].

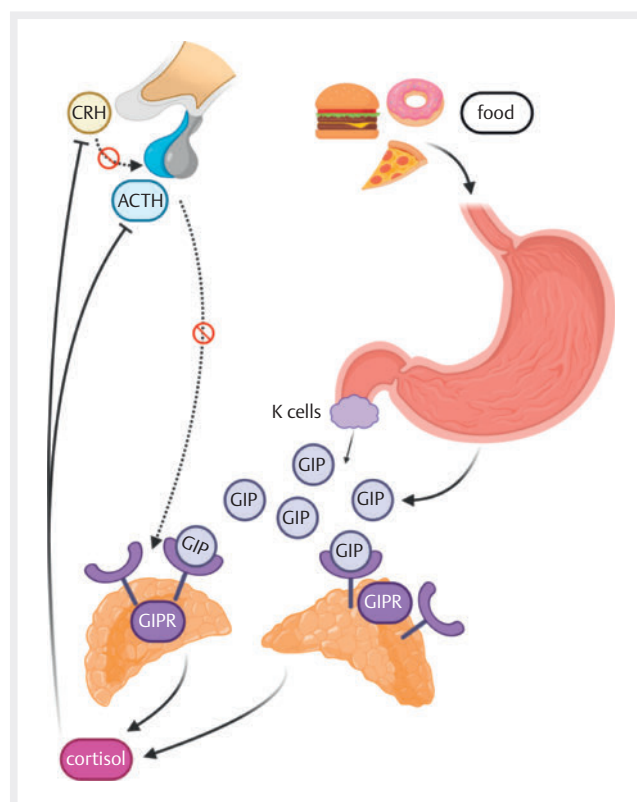
Glucose-dependent insulinotropic peptide, glucose-dependent insulinotropic peptide receptor, and Cushing's syndrome

The first case of a food-dependent Cushing's syndrome was reported by Pavel Hamet in 1987, describing a 41-year-old man with clinical and biological adrenocorticotropin (ACTH)-independent hypercortisolism secondary to a unilateral adrenocortical adenoma. The special feature of this patient was his low fasting cortisol, increasing after food intake, suggesting that “a humoral factor induced by eating was responsible for the periodic hormonogenesis, directly stimulating the adrenal secretion of cortisol” [2]. That humoral factor was identified as GIP 5 years later in back-to-back publications by André Lacroix and Yves Reznik [18, 19], enlightened by an editorial from Prof Xavier Bertagna [20] in the New England Journal of Medicine. They both described the cases of two women in their 40s presenting PBMAH and severe ACTH-independent Cushing's syndrome characterized by a low fasting plasma cortisol, increasing in correlation with serum GIP variations following meals. In these two cases, cortisol secretion was stimulated by oral glucose load, lipid-rich or protein-rich meals, but not by intravenous glucose infusion. The involvement of GIP was corroborated by the stimulation of cortisol secretion

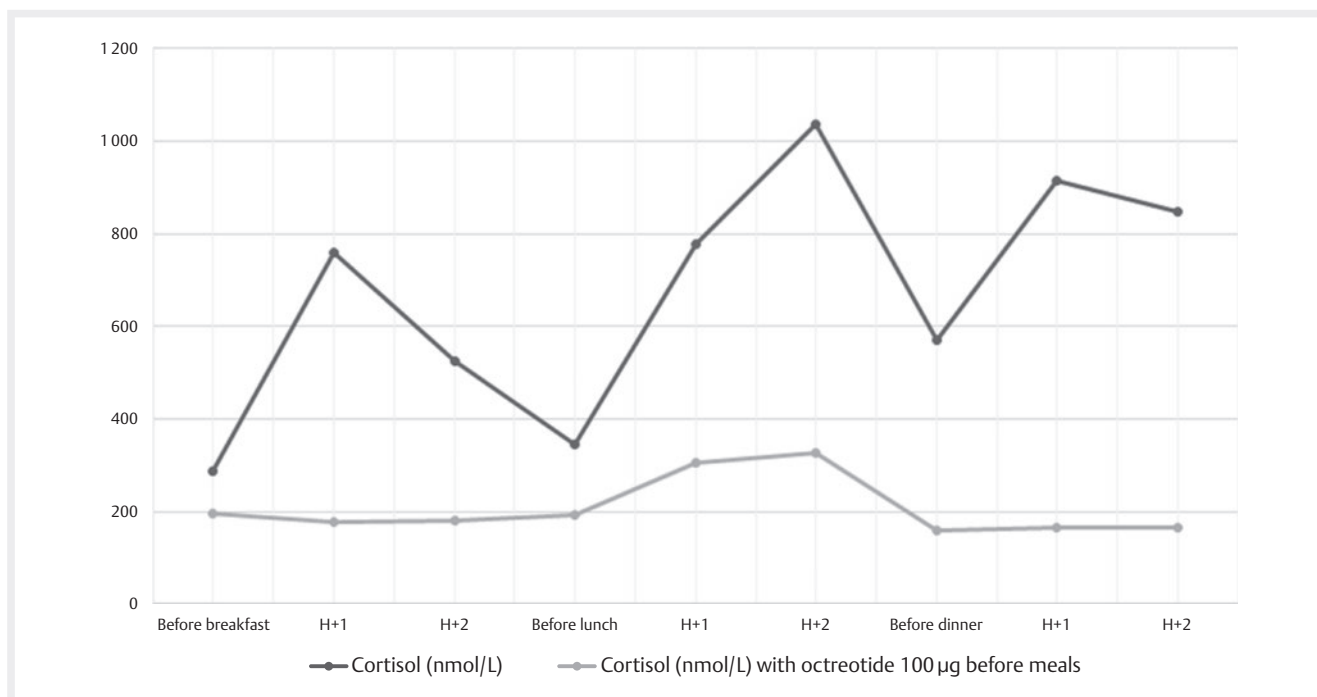
upon intravenous GIP infusion and suppressed by somatostatin analog treatment. The measured GIP was not higher in the two patients than in normal controls, not arguing for an excessive secretion of GIP but rather for an abnormal sensitivity of adrenocortical cells to the physiological postprandial increase of GIP. Based on previous descriptions of various hormone receptors in rat [21, 22] and human adrenocortical cancer [23], paving the way for the new concept of illegitimate receptor expression, both publications from Lacroix and Reznik assumed the role of the GIPR in food-dependent Cushing's syndrome [18, 19]. However, they were not able to demonstrate this since GIPR had not yet been cloned. Evidence for the abnormal expression of GIPR in food-dependent adenoma [24] and PBMAH [25, 26] was provided a few years later.

To summarize, in FDACS, the aberrantly expressed GIPR in adrenocortical cells is triggered when bound to GIP, which is physiologically secreted by duodenal K cells following food intake. This leads to the activation of the cAMP/PKA pathway, resulting in the stimulation of glucocorticoid synthesis (► Fig. 1), similar to ACTH stimulation. Chronic hypercortisolism consecutive to the intermittent but sustained GIP stimulation suppresses ACTH secretion, accounting for the low ACTH and cortisol levels during fast.

Whether or not GIPR ectopic expression in adrenocortical cells is sufficient to promote tumorigenesis is still a matter of question. An el-



► **Fig. 1** Schematic representation of food-dependent Cushing's syndrome pathophysiology. GIP is secreted by duodenal K cells in response to food intake. GIP binds to its receptor (GIPR) aberrantly expressed in adrenocortical cells and activates the cAMP/PKA pathway, resulting in a stimulation of cortisol secretion following meals. The cortisol excess suppresses CRH and ACTH secretion, accounting for the low plasma levels during fast. GIP, glucose-dependent insulinotropic polypeptide; GIPR, GIP receptor; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropin hormone. Created with BioRender.com. [rerif]



► **Fig. 2** Cortisol secretion in a patient with PBMAH and food-dependent Cushing's syndrome. This patient with food-dependent Cushing's syndrome has a low fasting cortisolemia <300 nmol/L, which dramatically increases quickly after food intake (dark line). The cortisol response following meals is suppressed by the subcutaneous injection of 100 µg octreotide before meals (pale line). PBMAH, primary bilateral macronodular adrenal hyperplasia.

ement of response was brought by Mazzuco and colleagues in 2007: a rat *Gipr* vector was transfected in bovine adrenocortical cells, and these cells were transplanted in adrenalectomized immunodeficient mice, resulting in the development of a hyperplastic adrenocortical tissue with a high GIP-responsive cortisol output, but non-responsive to ACTH. These observations account for the tumorigenic potential of aberrant expression of GIPR in adrenocortical cells [27].

FDCS was the first *in vivo* demonstration of the regulation of adrenocortical steroidogenesis by illegitimate GPCR, responding to physiological stimuli. Since then, many other GPCRs have been described in PBMAH, including vasopressin receptors AVPR1A and AVPR2 (cortisol response to upright posture and vasopressin agonists) [28–30], beta1 and beta2-adrenergic receptors (cortisol response to upright posture, sport, stress, etc.) [31], serotonin receptors 5HT4 (cortisol response to 5HT4 serotonin receptor agonists) [32–36], luteinizing hormone (LH) and human chorionic gonadotropin (LH/hCG) receptor (cortisol response to high LH in menopause, and probably to high hCG in pregnancy) [32, 37]; there are also some reports on aberrant response of PBMAH to thyroid stimulating hormone, glucagon, or follicle-stimulating hormone [38–40].

Diagnosis of food-dependent Cushing's syndrome

FDCS can be observed in unilateral adrenal Cushing's syndrome secondary to adrenocortical adenoma, or, more frequently, in PBMAH.

Some teams have reported the systematic screening of aberrant cortisol response to various stimuli in PBMAH, showing a high prevalence > 80 % of at least one illegitimate receptor, the most frequent being vasopressin receptors (33–75 %), beta-adrenergic receptors (33–48 %), serotonin receptors (16–47 %), GIP receptor (8–33 %), and LH/hCG receptor (around 15 %) [38–41]. However, concerning GIPR, this could be overestimated by a recruitment bias, and in retrospect, its prevalence is probably much lower and remains currently unknown. To the best of our knowledge, only 39 patients with PBMAH and FDCS have been reported in the literature and have been summarized by André Lacroix in 2023 [42]. Among them, 36 (92.3 %) were women, which is much higher imbalance than in other forms of PBMAH (65–70 % of women in sporadic PBMAH and around 50 % in PBMAH secondary to *ARMC5* germline mutation) [43–45].

The food-dependent nature of an adrenal Cushing's syndrome can be suspected in front of clinical signs of hypercortisolism with a surprisingly low morning fasting cortisolemia, associated with a suppressed circulating ACTH, which can mimic a corticotroph deficiency and an increasing cortisolemia during the diurnal cycle of measurements. It can be further corroborated by the stimulation of the cortisol secretion, indicated by an increase of 50 % or more of plasma and/or salivary cortisol after a mixed meal or oral glucose load following an overnight fasting (► **Fig. 2**). As somatostatin counteracts GIP action, the use of a somatostatin analog such as subcutaneous octreotide 100 µg before meals can show a decrease in cortisol stimulation after food intake [19] (► **Fig. 2**). Through intravenous GIP infusion, it is feasible to demonstrate the GIP-dependence of cortisol secretion [18, 19], but it is probably unneces-

sary for the diagnosis since GIPR is the only incretin receptor known to be aberrantly expressed in PBMAH. Notably, there is no report on the aberrant expression of the GLP1R in adrenal Cushing's syndrome [42].

Most patients with FDCS have been reported with a low fasting cortisol [3, 4]. However, one must consider the potential association of several illegitimate receptors in one patient, i. e., GIPR and LHCGR, which could lead to non-suppressed fasting cortisol due to the concomitant stimulation of cortisol secretion by several ligands [46].

The other biological assays meet the classical diagnostic methodology of any ACTH-independent Cushing's syndrome, including 24-h urinary free cortisol (24 h UFC) and 1 mg overnight or low dose dexamethasone suppression test (DST) [47]. Theoretically, DST could be faulted in FDCS due to the expected low morning fasting plasma cortisol in this situation [46]. However, in our experience, even if morning plasma cortisol is lower than in other forms of PBMAH, it is not fully suppressed, and since ACTH is usually already suppressed, the DST is not supposed to lower cortisol.

Several teams in the past have proposed, described, and performed systematic *in vivo* screening of illegitimate receptors in PBMAH patients [1, 38–41, 48]. However, considering the complexity of these time-consuming protocols, they are infrequently performed nowadays. Indeed, given that efficient specific treatments are available only for a limited number of receptors (mainly LHCGR and beta-adrenergic receptors) and that an individual patient often presents an aberrant response to a combination of illegitimate receptors, the added value of the results of these explorations in clinical practice at present is not demonstrated [46].

Treatment of food-dependent Cushing's syndrome

The treatment of the rare adrenocortical adenomas with FDCS is unilateral adrenalectomy [42], with a consecutive corticotroph deficiency necessitating glucocorticoid replacement until the recovery of corticotroph function. Bilateral adrenalectomy is the classical treatment of food-dependent PBMAH [42], with a following adrenal insufficiency needing lifelong glucocorticoid and mineralocorticoid replacement therapy. For a few decades, unilateral adrenalectomy has been considered in PBMAH to avoid lifelong medical treatment and to prevent the risk of adrenal crisis [49, 50]. Its use has been summarized in a recent review [46]: of the 286 reported patients with PBMAH treated with unilateral adrenalectomy, 220 (77 %) experienced an initial remission of Cushing's syndrome, with a secondary relapse of hypercortisolism in 64 (29 %), while 66 (23 %) had a persistent hypercortisolism after surgery. In total, 89 patients (31 %) further needed a contralateral adrenalectomy. Considering the rarity of FDCS, unilateral adrenalectomy has not been specifically studied in this condition yet [42]. However, we can speculate that in the persistent presence of the stimulus of cortisol secretion, namely GIP, removing one adrenal gland may not lead to the remission of Cushing's syndrome, as observed in ACTH-dependent Cushing's syndrome. Still, unilateral adrenalectomy may be considered in very asymmetrical food-dependent PBMAH with one morphologically dominant adrenal gland. To il-

lustrate this, André Lacroix recently reported that a patient with severe FDCS and very asymmetrical adrenals (two supra-centimetric nodules in the right adrenal and one infra-centimetric nodule in the left adrenal, with an exclusive iodocholesterol uptake by the right adrenal) [51] was still in remission 23 years after a right adrenalectomy [42]. This patient was further genotyped and harbored a germline *KDM1A* pathogenic variant associated with a 1p loss of heterozygosity in her right adrenal nodules [4].

Medical therapy by inhibitors of cortisol synthesis, such as metyrapone, ketoconazole, mitotane or the more recent osilodrostat, can be an alternative to the surgical treatment for patients for whom surgery is contra-indicated or refused [46]. These drugs may also be transiently used to prepare for surgery in case of severe hypercortisolism.

Considering the neutralization of GIP action by somatostatin, specific medical treatment of FDCS by somatostatin analogs has been reported [19, 24, 52–55], but usually with a transient control of cortisol secretion because GIP inhibition escapes after a few weeks or months or the rapid occurrence of side effects, limiting its use in clinical practice. Future prospects on the potential use of specific GIPR antagonists in FDCS would be valuable [42].

Clinical practitioners may advise FDCS patients against fasting, given that cortisol secretion is dependent on GIP and limited to GIP due to the suppressed CRH and ACTH in FDCS. Indeed, in the absence of GIP, the actual situation of a patient with FDCS is corticotroph deficiency, which could lead to an adrenal crisis in case of prolonged fasting. One also should consider a transient glucocorticoid replacement in case of medically justified fasting (i. e., before surgery).

Molecular causes of food-dependent Cushing's syndrome

Following the identification of germline *ARMC5* pathogenic variants in 2013 [56], its systematic sequencing has been performed in many different series of patients with PBMAH, with a mutation rate around 20 to 25 % in apparently sporadic index cases [43–45, 57]. Aberrant expression of illegitimate receptors in *ARMC5* mutated patients—mostly vasopressin, beta-adrenergic, and serotonin receptors—has been previously reported in the same proportion as in wild-type patients [44, 56, 58]. But none of the explored patients with FDCS, including those with a familial history of PBMAH, harbored an *ARMC5* pathogenic variant, suggesting a different genetic mechanism [3, 59, 60]. No pathogenic variant affecting the coding sequence of the *GIPR* gene or its promoter was identified in patients with FDCS [26, 61].

In 2017, Lecoq et al. reported the first large molecular study of both food-dependent adenomas and PBMAH. They found somatic microduplications and chromosomal rearrangements of the 19q13 region where the *GIPR* locus is mapped in 2/5 adrenocortical adenomas from patients with FDCS, and a complete 19q duplication in the nodular tissue from 1/10 patients with a food-dependent PBMAH. Those chromosomal alterations were absent in germline DNA [62].

In 2021, the genetic cause of food-dependent PBMAH was identified simultaneously by two independent teams, solving a 35-year

enigma. Our group used a multi-omics approach to classify 52 tumor samples from 36 adrenalectomized index cases of PBMAH with various phenotypes [3]. The integrative analysis revealed three different molecular groups: G1, comprising the tumor samples from the 16 patients with *ARMC5* mutation; G2, comprising the tumor samples from the six patients with FDCS; G3, from 14 more heterogeneous patients. *ARMC5* patients were characterized by a strong transcriptomic clustering and their recurrent copy-neutral 16p loss-of-heterozygosity (LOH), previously described as the second hit causing biallelic inactivation of the gene [56, 63]. All patients from the G2 group had a somatic loss of 1p arm, a high *GIPR* expression, and the most underexpressed gene compared to G1 and G3 was *KDM1A*, interestingly mapped at 1p. We then performed a germline exome sequencing and found a heterozygous pathogenic variant of *KDM1A* in 5/6 G2 patients. Combined with the loss of the wild-type allele through the 1p LOH, this led to the complete loss of *KDM1A* in the adrenal nodules, both at mRNA and protein levels. In addition, we found germline pathogenic variants of *KDM1A* in four supplementary index cases of food-dependent PBMAH, including one in a familial presentation. *KDM1A* mutated PBMAH were also distinguished by an unusually high proportion of eosinophilic cells; this aspect has been further explored and described recently in the first histopathological classification of PBMAH [64]. We did not find any recurrent germline or somatic alteration in the G3 group.

On their side, after the joint groups of Peter Kamenicky and Isabelle Bourdeau found *KDM1A* germline variants in two independent patients from their respective teams, they reported the same observations of *KDM1A* germline variants associated with somatic 1p LOH on 17 index cases of FDCS, and also in 2 familial situations [4]. In addition, they showed that both the combined use of a *KDM1A* siRNA with a pharmacological inhibitor of *KDM1A* (GSK-LSD1) and *KDM1A* knockout by CRISPR-Cas9 genome editing resulted in an increase of *GIPR* expression in the adrenocortical cell line H295R. They also described foci of myelolipoma in four patients and myeloid metaplasia in three others, which has not been observed in our series. In both studies, no *KDM1A* germline variant was reported in non-FDCS PBMAH control patients [3, 4].

KDM1A encodes a histone demethylase, demethylating histone 3 on lysine 4, and thus is considered a transcriptional repressor [65, 66]. We can speculate that a functional *KDM1A* normally represses *GIPR* transcription in adrenocortical cells and that this inhibition is lost in the case of *KDM1A* inactivation, leading to the aberrant expression of *GIPR*. However, *KDM1A* can also demethylate histone 3 on lysine 9, making it a transcriptional activator [67, 68]. Thus, the mechanisms through which *KDM1A* inactivation results in the *GIPR* overexpression in the adrenal cortex could be more complex.

Besides *GIPR*, we have demonstrated that *LHCGR*, encoding the LH and hCG receptor, was the second most overexpressed illegitimate receptor in tumor samples from *KDM1A* mutated patients, compared to G1 et G3 samples [3], this overexpression was also observed in H295R cells after *KDM1A* silencing [4]. A cortisol aberrant response mediated by *GIPR* and *LHCGR* concomitantly, had been previously reported in two unrelated PBMAH female patients [69], and one of our patients had a clear response to both mixed meal and GnRH, but none of the studied patients were known to

have clinical signs of Cushing's syndrome during pregnancy or after menopause. Larose et al., in 2019, also reported a patient with aberrant regulation of cortisol secretion by both *GIP* and *LH* [55].

Before the identification of *KDM1A* in FDCS, *KDM1A* germline variants had been reported in patients with multiple myeloma and monoclonal gammopathy of uncertain significance (MGUS, a premalignant condition predisposing to multiple myeloma) [70]. One of our *KDM1A* patients had a MGUS, and one other had a familial history of multiple myeloma in numerous relatives [3, 4]. Besides germline alterations in multiple myeloma, the overexpression of *KDM1A* has been demonstrated in different types of cancers [71]. Chasseloup et al. described some other malignancies in *KDM1A* patients (one rectal cancer, one bronchial neuroendocrine tumor, and one breast cancer) [4], but at this point, no functional data supports the involvement of *KDM1A* in the occurrence of these cancers.

Based on these data, the germline *KDM1A* sequencing should be proposed to every patient with PBMAH with arguments for an FDCS, such as low fasting cortisol or cortisol response to oral glucose load or mixed meal, as well as to every first-degree relative of *KDM1A* pathogenic variant carrier [42, 46]. Considering its association with multiple myeloma, *KDM1A* patients should also be monitored regularly for this disease, notably by serum protein electrophoresis. Subject to further investigations, *KDM1A* inactivation may be seen as the cause of a new syndromic disease rather than a predisposition to isolated food-dependent PBMAH.

The aberrant expression of *GIPR* has also been reported in around 30% of somatotroph pituitary adenomas, resulting in a paradoxical increase of GH after oral glucose load [72–75]. Chasseloup et al. recently sequenced *KDM1A* and other members of the large histone demethylases family in somatic DNA from 146 somatotropinomas. They did not identify any pathogenic variant. However, they observed recurrent 1p LOH and monoallelic *KDM1A* expression in the somatic DNA from 27.9% of adenomas, with a more frequent increase in *GIPR* expression in these adenomas, but this was neither constant nor exclusive, including with regard to the paradoxical response to oral glucose load. They concluded that *KDM1A* is not the molecular cause of *GIPR* expression in somatotropinomas [76].

Perspectives

In 2021, the identification of germline *KDM1A* mutations marked a turning point in the 35-year history of food-dependent Cushing's syndrome [3, 4], reinforcing the idea that PBMAH is a genetic disease [77], and leading to significant changes in clinical practice [42, 46]. Routine germline *KDM1A* testing can now be proposed to PBMAH patients with evidence for FDCS and to all first-degree relatives of *KDM1A* pathogenic variant carriers. Clinicians should also be aware of the risk of associated MGUS or multiple myeloma and screen their patients accordingly. It also proves that *in vivo* screening of aberrant *GIPR* expression, which could have been regarded as outdated in recent years, is actually essential to screen for FDCS and *KDM1A* alterations in patients with PBMAH.

These original findings broadened our knowledge on PBMAH and adrenal physiology in general, but they also have raised a number of unsolved questions: how to explain the large female pre-

dominance of FDCS? Do male variant carriers have an attenuated adrenal phenotype or no phenotype at all, and for what reasons? Considering the critical role of *KDM1A* in human embryonic stem cells and its ubiquitous expression [78, 79], why does its constitutive inactivation seem to only affect adrenals and plasma cells? Hence, *KDM1A* identification not only has clinical consequences, but also several exhilarating scientific implications with numerous interrogations to address.

Conflict of Interest

Research grant and board honoraria from HRA and Recordati RD to J Bertherat or its institution

References

- [1] Lacroix A, Ndiaye N, Tremblay J et al. Ectopic and abnormal hormone receptors in adrenal Cushing's syndrome. *Endocr Rev* 2001; 22: 75–110. DOI: 10.1210/edrv.22.1.0420
- [2] Hamet P, Laroche P, Franks DJ et al. Cushing syndrome with food-dependent periodic hormonogenesis. *Clin Invest Med* 1987; 10: 530–533
- [3] Vaczlavik A, Bouys L, Violon F et al. *KDM1A* inactivation causes hereditary food-dependent Cushing syndrome. *Genet Med* 2022; 24: 374–383. DOI: 10.1016/j.gim.2021.09.018
- [4] Chasseloup F, Bourdeau I, Tabarin A et al. Loss of *KDM1A* in GIP-dependent primary bilateral macronodular adrenal hyperplasia with Cushing's syndrome: A multicentre, retrospective, cohort study. *Lancet Diabetes Endocrinol* 2021; 9: 813–824. DOI: 10.1016/S2213-8587(21)00236-9
- [5] Marks V. The early history of GIP 1969–2000: From enterogastrone to major metabolic hormone. *Peptides* 2020; 125: 170276. DOI: 10.1016/j.peptides.2020.170276
- [6] Brown JC, Pederson RA, Jorpes E et al. Preparation of highly active enterogastrone. *Can J Physiol Pharmacol* 1969; 47: 113–114. DOI: 10.1139/y69-020
- [7] Turner DS, Shabaan A, Etheridge L et al. The effect of an intestinal polypeptide fraction on insulin release in the rat in vitro and in vivo. *Endocrinology* 1973; 93: 1323–1328. DOI: 10.1210/endo-93-6-1323
- [8] McIntyre N, Holdsworth CD, Turner DS. New interpretation of oral glucose tolerance. *Lancet* 1964; 2: 20–21. DOI: 10.1016/S0140-6736(64)90011-x
- [9] Dupre J. An intestinal hormone affecting glucose disposal in man. *Lancet* 1964; 2: 672–673. DOI: 10.1016/S0140-6736(64)92481-x
- [10] Laughton NB, Macallum AB, Macallum AB. The relation of the duodenal mucosa to the internal secretion of the pancreas. *Proc R Soc Lond B* 1997; 111: 37–46. DOI: 10.1098/rspb.1932.0042
- [11] Turner DS, Etheridge L, Marks V et al. Effectiveness of the intestinal polypeptides, IRP, GIP, VIP and motilin on insulin release in the rat. *Diabetologia* 1974; 10: 459–463. DOI: 10.1007/BF01221638
- [12] Dupre J, Ross SA, Watson D et al. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. *J Clin Endocrinol Metab* 1973; 37: 826–828. DOI: 10.1210/jcem-37-5-826
- [13] Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: Similarities and differences. *J Diabetes Investig* 2010; 1: 8–23. DOI: 10.1111/j.2040-1124.2010.00022.x
- [14] Yamada Y, Hayami T, Nakamura K et al. Human gastric inhibitory polypeptide receptor: Cloning of the gene (GIPR) and cDNA. *Genomics* 1995; 29: 773–776. DOI: 10.1006/geno.1995.9937
- [15] Volz A, Göke R, Lankat-Buttgereit B et al. Molecular cloning, functional expression, and signal transduction of the GIP-receptor cloned from a human insulinoma. *FEBS Lett* 1995; 373: 23–29. DOI: 10.1016/0014-5793(95)01006-z
- [16] Gremlich S, Porret A, Hani EH et al. Cloning, functional expression, and chromosomal localization of the human pancreatic islet glucose-dependent insulinotropic polypeptide receptor. *Diabetes* 1995; 44: 1202–1208. DOI: 10.2337/diab.44.10.1202
- [17] Mayendraraj A, Rosenkilde MM, Gasbjerg LS. GLP-1 and GIP receptor signaling in beta cells - A review of receptor interactions and co-stimulation. *Peptides* 2022; 151: 170749. DOI: 10.1016/j.peptides.2022.170749
- [18] Lacroix A, Bolté E, Tremblay J et al. Gastric inhibitory polypeptide-dependent cortisol hypersecretion--a new cause of Cushing's syndrome. *N Engl J Med* 1992; 327: 974–980. DOI: 10.1056/NEJM199210013271402
- [19] Reznik Y, Allali-Zerah V, Chayvialle JA et al. Food-dependent Cushing's syndrome mediated by aberrant adrenal sensitivity to gastric inhibitory polypeptide. *N Engl J Med* 1992; 327: 981–986. DOI: 10.1056/NEJM199210013271403
- [20] Bertagna X. New Causes of Cushing's Syndrome. *New England Journal of Medicine* 1992; 327: 1024–1025. DOI: 10.1056/NEJM199210013271410
- [21] Schorr I, Ney RL. Abnormal hormone responses of an adrenocortical cancer adenyl cyclase. *J Clin Invest* 1971; 50: 1295–1300. DOI: 10.1172/JCI106608
- [22] Schorr I, Rathnam P, Saxena BB et al. Multiple specific hormone receptors in the adenylate cyclase of an adrenocortical carcinoma. *J Biol Chem* 1971; 246: 5806–5811
- [23] Hingshaw HT, Ney RL, McKerns KW. Abnormal control in the neoplastic adrenal cortex. *Hormones and Cancer* 1974; 309–327
- [24] de Herder WW, Hofland LJ, Usdin TB et al. Food-dependent Cushing's syndrome resulting from abundant expression of gastric inhibitory polypeptide receptors in adrenal adenoma cells. *J Clin Endocrinol Metab* 1996; 81: 3168–3172. DOI: 10.1210/jcem.81.9.8784063
- [25] Luton JP, Bertherat J, Kuhn JM et al. Aberrant expression of the GIP (Gastric Inhibitory Polypeptide) receptor in an adrenal cortical adenoma responsible for a case of food-dependent Cushing's syndrome. *Bull Acad Natl Med* 1998; 182: 1839–1849. discussion 1849-1850
- [26] N'Diaye N, Tremblay J, Hamet P et al. Adrenocortical overexpression of gastric inhibitory polypeptide receptor underlies food-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 1998; 83: 2781–2785. DOI: 10.1210/jcem.83.8.5038
- [27] Mazzucco TL, Chabre O, Feige JJ et al. Aberrant GPCR expression is a sufficient genetic event to trigger adrenocortical tumorigenesis. *Mol Cell Endocrinol* 2007; 265–266: 23–28. DOI: 10.1016/j.mce.2006.12.034
- [28] Lacroix A, Tremblay J, Touyz RM et al. Abnormal adrenal and vascular responses to vasopressin mediated by a V1-vasopressin receptor in a patient with adrenocorticotropin-independent macronodular adrenal hyperplasia, Cushing's syndrome, and orthostatic hypotension. *J Clin Endocrinol Metab* 1997; 82: 2414–2422. DOI: 10.1210/jcem.82.8.4140
- [29] Mune T, Murase H, Yamakita N et al. Eutopic overexpression of vasopressin v1a receptor in adrenocorticotropin-independent macronodular adrenal hyperplasia. *J Clin Endocrinol Metab* 2002; 87: 5706–5713. DOI: 10.1210/jc.2002-020067
- [30] Louiset E, Contesse V, Groussin L et al. Expression of vasopressin receptors in ACTH-independent macronodular bilateral adrenal hyperplasia causing Cushing's syndrome: Molecular, immunohistochemical and pharmacological correlates. *J Endocrinol* 2008; 196: 1–9. DOI: 10.1677/JOE-07-0413

- [31] Lacroix A, Tremblay J, Rousseau G et al. Propranolol therapy for ectopic beta-adrenergic receptors in adrenal Cushing's syndrome. *N Engl J Med* 1997; 337: 1429–1434. DOI: 10.1056/NEJM199711133372004
- [32] Lacroix A, Hamet P, Boutin JM. Leuprolide acetate therapy in luteinizing hormone--dependent Cushing's syndrome. *N Engl J Med* 1999; 341: 1577–1581. DOI: 10.1056/NEJM199911183412104
- [33] Cartier D, Lihmann I, Parmentier F et al. Overexpression of serotonin₄ receptors in cisapride-responsive adrenocorticotropin-independent bilateral macronodular adrenal hyperplasia causing Cushing's syndrome. *J Clin Endocrinol Metab* 2003; 88: 248–254. DOI: 10.1210/jc.2002-021107
- [34] Mannelli M, Ferruzzi P, Luciani P et al. Cushing's syndrome in a patient with bilateral macronodular adrenal hyperplasia responding to cisapride: An in vivo and in vitro study. *J Clin Endocrinol Metab* 2003; 88: 4616–4622. DOI: 10.1210/jc.2002-021949
- [35] Contesse V, Reznik Y, Louiset E et al. Abnormal sensitivity of cortisol-producing adrenocortical adenomas to serotonin: In vivo and in vitro studies. *J Clin Endocrinol Metab* 2005; 90: 2843–2850. DOI: 10.1210/jc.2004-2476
- [36] Vezzosi D, Cartier D, Régnier C et al. Familial adrenocorticotropin-independent macronodular adrenal hyperplasia with aberrant serotonin and vasopressin adenoreceptors. *Eur J Endocrinol* 2007; 156: 21–31. DOI: 10.1530/eje.1.02324
- [37] Plöckinger U, Chrusciel M, Doroszko M et al. Functional implications of LH/hCG receptors in pregnancy-induced Cushing syndrome. *J Endocr Soc* 2017; 1: 57–71. DOI: 10.1210/js.2016-1021
- [38] Hsiao H-P, Kirschner LS, Bourdeau I et al. Clinical and genetic heterogeneity, overlap with other tumor syndromes, and atypical glucocorticoid hormone secretion in adrenocorticotropin-independent macronodular adrenal hyperplasia compared with other adrenocortical tumors. *J Clin Endocrinol Metab* 2009; 94: 2930–2937. DOI: 10.1210/jc.2009-0516
- [39] Libé R, Coste J, Guignat L et al. Aberrant cortisol regulations in bilateral macronodular adrenal hyperplasia: A frequent finding in a prospective study of 32 patients with overt or subclinical Cushing's syndrome. *Eur J Endocrinol* 2010; 163: 129–138. DOI: 10.1530/EJE-10-0195
- [40] Hofland J, Hofland LJ, van Koetsveld PM et al. ACTH-independent macronodular adrenocortical hyperplasia reveals prevalent aberrant in vivo and in vitro responses to hormonal stimuli and coupling of arginine-vasopressin type 1a receptor to 11 β -hydroxylase. *Orphanet J Rare Dis* 2013; 8: 142. DOI: 10.1186/1750-1172-8-142
- [41] Mircescu H, Jilwan J, N'Diaye N et al. Are ectopic or abnormal membrane hormone receptors frequently present in adrenal Cushing's syndrome? *J Clin Endocrinol Metab* 2000; 85: 3531–3536. DOI: 10.1210/jcem.85.10.6865
- [42] Lacroix A. Extensive expertise in endocrinology: Glucose-dependent insulinotropic peptide-dependent Cushing's syndrome. *Eur J Endocrinol* 2023; 188: R56–R72. DOI: 10.1093/ejendo/lvad026
- [43] Faucz FR, Zilbermint M, Lodish MB et al. Macronodular adrenal hyperplasia due to mutations in an armadillo repeat containing 5 (ARMC5) gene: A clinical and genetic investigation. *J Clin Endocrinol Metab* 2014; 99: E1113–E1119. DOI: 10.1210/jc.2013-4280
- [44] Espiard S, Drougat L, Libé R et al. ARMC5 mutations in a large cohort of primary macronodular adrenal hyperplasia: Clinical and functional consequences. *J Clin Endocrinol Metab* 2015; 100: E926–E935. DOI: 10.1210/jc.2014-4204
- [45] Bouys L, Vaczlavik A, Jouinot A et al. Identification of predictive criteria for pathogenic variants of primary bilateral macronodular adrenal hyperplasia (PBMAH) gene ARMC5 in 352 unselected patients. *Eur J Endocrinol* 2022; 187: 123–134. DOI: 10.1530/EJE-21-1032
- [46] Bertherat J, Bourdeau I, Bouys L et al. Clinical, pathophysiologic, genetic, and therapeutic progress in primary bilateral macronodular adrenal hyperplasia. *Endocr Rev* 2023; 44: 567–628. DOI: 10.1210/edrv/bnac034
- [47] Bouys L, Chiodini I, Arlt W et al. Update on primary bilateral macronodular adrenal hyperplasia (PBMAH). *Endocrine* 2021; 71: 595–603. DOI: 10.1007/s12020-021-02645-w
- [48] Lacroix A, Mircescu H, Harriet P. Clinical evaluation of the presence of abnormal hormone receptors in adrenal Cushing's syndrome. *The Endocrinologist* 1999; 9: 9
- [49] Debillon E, Velayoudom-Cephise F-L, Salenave S et al. Unilateral adrenalectomy as a first-line treatment of Cushing's syndrome in patients with primary bilateral macronodular adrenal hyperplasia. *J Clin Endocrinol Metab* 2015; 100: 4417–4424. DOI: 10.1210/jc.2015-2662
- [50] Meloche-Dumas L, Mercier F, Lacroix A. Role of unilateral adrenalectomy in bilateral adrenal hyperplasias with Cushing's syndrome. *Best Pract Res Clin Endocrinol Metab* 2021; 35: 101486. DOI: 10.1016/j.beem.2021.101486
- [51] N'Diaye N, Hamet P, Tremblay J et al. Asynchronous development of bilateral nodular adrenal hyperplasia in gastric inhibitory polypeptide-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 1999; 84: 2616–2622. DOI: 10.1210/jcem.84.8.5930
- [52] Lebrethon MC, Avallet O, Reznik Y et al. Food-dependent Cushing's syndrome: Characterization and functional role of gastric inhibitory polypeptide receptor in the adrenals of three patients. *J Clin Endocrinol Metab* 1998; 83: 4514–4519. DOI: 10.1210/jcem.83.12.5336
- [53] Albiger NM, Occhi G, Mariniello B et al. Food-dependent Cushing's syndrome: From molecular characterization to therapeutic results. *Eur J Endocrinol* 2007; 157: 771–778. DOI: 10.1530/EJE-07-0253
- [54] Preumont V, Mermejo LM, Damoiseaux P et al. Transient efficacy of octreotide and pasireotide (SOM230) treatment in GIP-dependent Cushing's syndrome. *Horm Metab Res* 2011; 43: 287–291. DOI: 10.1055/s-0030-1270523
- [55] Larose S, Bondaz L, Mermejo LM et al. Coexistence of myelolipoma and primary bilateral macronodular adrenal hyperplasia with GIP-dependent Cushing's syndrome. *Front Endocrinol (Lausanne)* 2019; 10: 618. DOI: 10.3389/fendo.2019.00618
- [56] Assié G, Libé R, Espiard S et al. ARMC5 mutations in macronodular adrenal hyperplasia with Cushing's syndrome. *N Engl J Med* 2013; 369: 2105–2114. DOI: 10.1056/NEJMoa1304603
- [57] Alencar GA, Lerario AM, Nishi MY et al. ARMC5 mutations are a frequent cause of primary macronodular adrenal hyperplasia. *J Clin Endocrinol Metab* 2014; 99: E1501–E1509. DOI: 10.1210/jc.2013-4237
- [58] Bourdeau I, Oble S, Magne F et al. ARMC5 mutations in a large French-Canadian family with cortisol-secreting β -adrenergic/vasopressin responsive bilateral macronodular adrenal hyperplasia. *Eur J Endocrinol* 2016; 174: 85–96. DOI: 10.1530/EJE-15-0642
- [59] Drougat L, Espiard S, Bertherat J. Genetics of primary bilateral macronodular adrenal hyperplasia: A model for early diagnosis of Cushing's syndrome? *Eur J Endocrinol* 2015; 173: M121–M131. DOI: 10.1530/EJE-15-0532
- [60] Faillot S, Foulonneau T, Néou M et al. Genomic classification of benign adrenocortical lesions. *Endocr Relat Cancer* 2021; 28: 79–95. DOI: 10.1530/ERC-20-0128
- [61] Antonini SR, N'Diaye N, Baldacchino V et al. Analysis of the putative regulatory region of the gastric inhibitory polypeptide receptor gene in food-dependent Cushing's syndrome. *J Steroid Biochem Mol Biol* 2004; 91: 171–177. DOI: 10.1016/j.jsbmb.2004.03.120
- [62] Lecoq A-L, Stratakis CA, Viengchareun S et al. Adrenal GIPR expression and chromosome 19q13 microduplications in GIP-dependent Cushing's syndrome. *JCI Insight* 2017; 2: e92184. 92184. DOI: 10.1172/jci.insight.92184

- [63] Correa R, Zilbermint M, Berthon A et al. The ARMC5 gene shows extensive genetic variance in primary macronodular adrenocortical hyperplasia. *Eur J Endocrinol* 2015; 173: 435–440. DOI: 10.1530/EJE-15-0205
- [64] Violon F, Bouys L, Berthon A et al. Impact of morphology in the genotype and phenotype correlation of bilateral macronodular adrenocortical disease (BMAD): A series of clinicopathologically well-characterized 35 cases. *Endocr Pathol* 2023; 34: 179–199. DOI: 10.1007/s12022-023-09751-7
- [65] Shi Y, Lan F, Matson C et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell* 2004; 119: 941–953. DOI: 10.1016/j.cell.2004.12.012
- [66] Vincier NK, Patel NA, Geusz RJ et al. LSD1-mediated enhancer silencing attenuates retinoic acid signalling during pancreatic endocrine cell development. *Nat Commun* 2020; 11: 2082. DOI: 10.1038/s41467-020-16017-x
- [67] Wang J, Scully K, Zhu X et al. Opposing LSD1 complexes function in developmental gene activation and repression programmes. *Nature* 2007; 446: 882–887. DOI: 10.1038/nature05671
- [68] Laurent B, Ruitu L, Murn J et al. A specific LSD1/KDM1A isoform regulates neuronal differentiation through H3K9 demethylation. *Mol Cell* 2015; 57: 957–970. DOI: 10.1016/j.molcel.2015.01.010
- [69] Bertherat J, Contesse V, Louiset E et al. In vivo and in vitro screening for illegitimate receptors in adrenocorticotropin-independent macronodular adrenal hyperplasia causing Cushing's syndrome: Identification of two cases of gonadotropin/gastric inhibitory polypeptide-dependent hypercortisolism. *J Clin Endocrinol Metab* 2005; 90: 1302–1310. DOI: 10.1210/jc.2004-1256
- [70] Wei X, Calvo-Vidal MN, Chen S et al. Germline lysine-specific demethylase 1 (LSD1/KDM1A) mutations confer susceptibility to multiple myeloma. *Cancer Res* 2018; 78: 2747–2759. DOI: 10.1158/0008-5472.CAN-17-1900
- [71] Karakaidos P, Verigos J, Magklara A. LSD1/KDM1A, a gate-keeper of cancer stemness and a promising therapeutic target. *Cancers* 2019; 11: 1821. DOI: 10.3390/cancers11121821
- [72] Hage M, Chaligné R, Viengchareun S et al. Hypermethylator phenotype and ectopic GIP receptor in GNAS mutation-negative somatotropinomas. *J Clin Endocrinol Metab* 2019; 104: 1777–1787. DOI: 10.1210/jc.2018-01504
- [73] Regazzo D, Losa M, Albiger NM et al. The GIP/GIPR axis is functionally linked to GH-secretion increase in a significant proportion of GSP-somatotropinomas. *Eur J Endocrinol* 2017; 176: 543–553. DOI: 10.1530/EJE-16-0831
- [74] Occhi G, Losa M, Albiger N et al. The glucose-dependent insulinotropic polypeptide receptor is overexpressed amongst GNAS1 mutation-negative somatotropinomas and drives growth hormone (GH)-promoter activity in GH3 cells. *J Neuroendocrinol* 2011; 23: 641–649. DOI: 10.1111/j.1365-2826.2011.02155.x
- [75] Hage M, Janot C, Salenave S et al. Management of endocrine disease: Etiology and outcome of acromegaly in patients with a paradoxical GH response to glucose. *Eur J Endocrinol* 2021; 184: R261–R268. DOI: 10.1530/EJE-20-1448
- [76] Chasseloup F, Regazzo D, Tosca L et al. KDM1A genotyping and expression in 146 sporadic somatotroph pituitary adenomas. *Eur J Endocrinol* 2024; 190: 173–181. DOI: 10.1093/ajendo/lvae013
- [77] Cavalcante IP, Berthon A, Fragoso MC et al. Primary bilateral macronodular adrenal hyperplasia: Definitely a genetic disease. *Nat Rev Endocrinol* 2022; 18: 699–711. DOI: 10.1038/s41574-022-00718-y
- [78] Metzger E, Wissmann M, Yin N et al. LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. *Nature* 2005; 437: 436–439. DOI: 10.1038/nature04020
- [79] Adamo A, Sesé B, Boue S et al. LSD1 regulates the balance between self-renewal and differentiation in human embryonic stem cells. *Nat Cell Biol* 2011; 13: 652–659. DOI: 10.1038/ncb2246