ACTH-Independent Macronodular Adrenal Hyperplasia 3 (AIMAH3) — Comprehensive Disease Report

Prepared for a disease knowledge-base entry. Evidence is human clinical / genetic unless otherwise stated. Primary citations are given as PMIDs.

Summary (Answer to the Research Question)

ACTH-independent Macronodular Adrenal Hyperplasia 3 (AIMAH3; OMIM #620990; MONDO:0700299) is a rare, autosomal-dominant Mendelian endocrine tumor-predisposition syndrome that is the genetically defined form of **food-dependent (GIP-dependent) Cushing syndrome (FDCS)**. It is caused by **germline heterozygous loss-of-function (truncating) variants in *KDM1A* (LSD1; chromosome 1p36; gene OMIM 609132)** combined with **somatic loss of the wild-type allele on 1p** in adrenal nodules — a two-hit tumor-suppressor mechanism. Biallelic *KDM1A* inactivation in adrenocortical cells permits **ectopic expression of the glucose-dependent insulinotropic polypeptide receptor (GIPR)**; meal-stimulated GIP (from duodenal K cells) then binds adrenal GIPR, activates cAMP/PKA, and drives **post-prandial cortisol hypersecretion**, producing ACTH-independent Cushing syndrome on a background of **bilateral macronodular adrenal hyperplasia**. It accounts for ~3.3% of all primary bilateral macronodular adrenal hyperplasia (PBMAH) index cases and ~90% of FDCS, shows a striking female predominance, and is definitively treated by adrenalectomy.

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1. Disease Information

- **Overview:** AIMAH3 is a subtype within the ACTH-independent macronodular adrenal hyperplasia phenotypic series in which bilateral, benign, large adrenocortical nodules autonomously secrete cortisol under the control of ingested food. It is the molecular

subtype of **food-dependent Cushing syndrome**. Individuals characteristically have **low fasting morning cortisol and low/suppressed ACTH but excess cortisol after eating**.

- **Key identifiers:**
- **OMIM:** #620990 (AIMAH3); phenotypic series **PS219080** (AIMAH). Gene *KDM1A* OMIM 609132.
- **MONDO:** MONDO:0700299
- **MedGen:** CN378661
- **MeSH:** the closest heading is Cushing Syndrome (D003480); "adrenal hyperplasia, macronodular" is indexed under adrenocortical hyperplasia. No AIMAH3-specific MeSH.
- **ICD-11:** 5A70 (Cushing syndrome) / 5A74.0 region for ACTH-independent Cushing; **ICD-10:** E24.0 (pituitary-dependent) is not applicable — adrenal Cushing is **E24.8/E24.9**; adrenal hyperplasia **E27.8**. No AIMAH3-specific code.
- **Orphanet:** Covered under "ACTH-independent macronodular adrenal hyperplasia" (ORPHA:189439 for PBMAH); no distinct AIMAH3 ORPHA code.
- **UniProt disease:** DI-06963.
- **Synonyms / alternative names:** AIMAH3; ACTH-independent macronodular adrenal hyperplasia 3; **Food-dependent Cushing syndrome (FDCS)**; **GIP-dependent Cushing syndrome**; GIP-dependent PBMAH; (broader, non-synonymous parent terms) primary bilateral macronodular adrenal hyperplasia (PBMAH), bilateral macronodular adrenal disease (BMAD).
- **Position within the AIMAH phenotypic series (PS219080):**

Subtype	OMIM #	Gene (OMIM)	Locus	Mechanism	Distinctive feature
AIMAH1	#219080	*GNAS* (139320)	20q13	**Somatic** activating mutation (R201H/ R201S; constitutive Gs)	Not McCune-Albright; mutation absent in blood
AIMAH2	#615954	*ARMC5* (615549)	16p11.2	Germline + somatic (**two-hit**)	Commonest genetic PBMAH (~20–25%); no food dependence
AIMAH3	**#620990**	***KDM1A* (609132)**	**1p36**	Germline + somatic (**two-hit**, 1p LOH)	**Food/GIP-dependent Cushing**

AIMAH patients typically present in the **5th–6th decade (~10 years later than other Cushing causes)**, and most cases are sporadic (OMIM PS219080; Assié 2013 identified ARMC5 in 18/33=55% of macronodular hyperplasia tumors; Chasseloup 2021 P 34655521 reported 17 GIP-dependent PBMAH cases with a recurrent 1p/KDM1A deletion). - **Data source type:** Information is derived from **aggregated disease-level genetic/clinical cohort studies and case series** (e.g., 301-case and 36-case multicentre cohorts) plus individual case reports — not from a single EHR dataset.

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2. Etiology

- **Primary cause — genetic:** Germline heterozygous **inactivating (truncating: frameshift/ nonsense) variants in *KDM1A***, with a **somatic second hit** (loss of heterozygosity / deletion of chromosome 1p bearing the wild-type allele) in adrenocortical lesions. "Exome sequencing revealed germline truncating variants of KDM1A … constantly associated with a somatic loss of the KDM1A wild-type allele on 1p, leading to a loss of KDM1A expression both at messenger RNA and protein levels" and "KDM1A inactivation explains about 90% of FDCS PBMAH" (P 34906447). This is a two-hit tumor-suppressor model (P 41864332).
- **Genetic risk factors:** The germline *KDM1A* LoF allele is the causal susceptibility factor; disease requires the acquired somatic 1p loss. No additional common susceptibility loci are established. *ARMC5* (AIMAH2/PBMAH1) is the differential genetic cause and is **mutually exclusive** with the FDCS phenotype (P 39921449).
- **Environmental risk factors / triggers:** The obligate physiological "trigger" is **food/meal intake**, which raises GIP and drives cortisol secretion. Female sex is a strong, unexplained risk marker (100% of KDM1A carriers were women in the largest cohort;

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P 39921449

No toxin, radiation, or occupational exposure is implicated.

- **Protective factors:** None established genetically or environmentally. Conceptually, avoiding the GIP–GIPR axis (e.g., fasting) transiently lowers cortisol but is not therapeutic. Somatic events being required means most heterozygous carriers may remain unaffected (incomplete penetrance).
- **Gene–environment interaction:** The defining GxE interaction is **KDM1A loss (genetic) × dietary GIP secretion (environmental/physiological)** → post-prandial hypercortisolism. Without the genetic lesion, food does not stimulate cortisol; without food, the genetic lesion produces little fasting cortisol excess.
- **Infectious agents:** Not applicable.

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3. Phenotypes

The clinical phenotype is that of **chronic endogenous cortisol excess (Cushing syndrome)**, but with a food-dependent secretory pattern. Onset is typically **adult** (commonly 4th–6th decades), insidious, and slowly progressive. Severity is variable (mild autonomous cortisol secretion → overt Cushing). Key phenotypes and suggested HPO terms:

Phenotype	Type	HPO term	Notes / frequency
Cushingoid habitus / truncal (central) obesity	physical sign	HP:0002591 (truncal obesity), HP:0001513 (obesity)	Common (OMIM clinical synopsis)
Facial fullness ("moon facies")	physical sign	HP:0000283	Common
Arterial hypertension	clinical sign	HP:0000822	Very common; PBMAH cohorts show high rates
Type 2 diabetes / glucose intolerance	lab/clinical	HP:0000857 / HP:0000833	Common (45% diabetes in PBMAH vs 25% non-PBMAH, P 35597729)
Abdominal striae	physical sign	HP:0001065 (Striae distensae)	Reported in OMIM synopsis
Proximal muscle weakness	symptom/ sign	HP:0003701 (proximal muscle weakness) / HP:0003324	From cortisol-induced myopathy
Osteoporosis	lab/imaging	HP:0000939	Reported
Hypercortisolemia / loss of diurnal rhythm	lab abnormality	HP:0003118 (abnormal circulating cortisol), HP:0003119 region	Defining; low AM/high PM cortisol
Suppressed ACTH (ACTH-independent)	lab abnormality	HP:0002920 (decreased ACTH)	Defining
Bilateral adrenal macronodular hyperplasia	imaging/ structural	HP:0008256 (Adrenal hyperplasia); HP:0031044 (adrenocortical hyperplasia)	Defining, bilateral
Elevated urinary free cortisol	lab abnormality	HP:0003564 (Hypercortisoluria)	3.0× ULN in KDM1A vs 1.36× ARMC5 (P 39921449)

- **Phenotype characteristics:** Adult-onset; severity mild→severe/variable; course chronic and slowly progressive; the biochemical hallmark is the **inverted cortisol rhythm** (low morning, high post-prandial/midnight). In the 301-case cohort, KDM1A patients had **higher 24h UFC (3.0× ULN), lower morning cortisol (192 vs 407/428 nmol/L), higher midnight cortisol (487 vs 297/172 nmol/L)** (P 39921449).
- **Quality-of-life impact:** As for other forms of Cushing syndrome — impaired physical function (myopathy, obesity, fractures), metabolic/cardiovascular morbidity, and neuropsychiatric effects (mood disturbance, cognitive complaints) reduce QoL; disease-specific QoL is measured with CushingQoL and generic SF-36/EQ-5D. No AIMAH3-specific QoL study exists (data gap).

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4. Genetic / Molecular Information

- **Causal gene:** ***KDM1A*** (lysine demethylase 1A; alias **LSD1, KDM1, AOF2**). HGNC:29079; NCBI Gene 23028; Ensembl ENSG00000004487; UniProt O60341. Gene OMIM 609132. Locus **1p36.12**.
- **Pathogenic variants:**
- **Classification:** Pathogenic / likely pathogenic per ACMG/AMP (P 39921449).
  VUS reported in broad incidentaloma panels (P 41113712).
- **Variant type/class:** Predominantly **truncating loss-of-function** — frameshift and nonsense (and splice) — germline (P 34906447).
  The second hit is a **somatic structural event (1p LOH/deletion)**.
- **Allele frequency:** Germline *KDM1A* LoF variants are rare in gnomAD (KDM1A is relatively loss-of-function intolerant); no common population variant. Disease-associated alleles are private/family-specific.

- **Somatic vs germline: Both** required — germline heterozygous LoF + somatic 1p loss (two-hit).
- **Functional consequence: Loss of function** (loss of KDM1A mRNA and protein in adrenal tissue; P 34906447), consistent with tumor-suppressor behavior (P 41864332).
- **Modifier genes:** None established. *ARMC5* status is mutually exclusive (defines AIMAH2).
- **Epigenetic information:** KDM1A/LSD1 is itself an **epigenetic eraser** — a histone demethylase for **H3K4me1/2 and H3K9me1/2** (P 38152966) with scaffolding control of DNA methylation (P 39237615). Its loss perturbs the adrenocortical chromatin/transcriptional landscape and is thought to permit **de-repression/ectopic transcription of *GIPR***. Multiomics profiling included methylome and miRNome analyses defining a distinct FDCS molecular group (P 34906447).
- **Chromosomal abnormalities: Somatic loss of chromosome 1p** (LOH) in adrenal nodules is the recurrent large-scale event (P 34906447). In the distinct *unilateral* GIP-adenoma route, **somatic 19q13.32 duplication/ rearrangement of the *GIPR* locus** occurs (P 36857084) — not AIMAH3.

5. Environmental Information

- **Environmental factors:** No toxin/radiation/pollution/occupational cause. The relevant "environmental" input is **dietary intake**, which triggers GIP secretion and hence cortisol release.
- **Lifestyle factors:** Meal composition/timing modulates GIP and therefore cortisol; oral (but not IV) glucose triggers cortisol
  (P 21264796).
  No smoking/alcohol association established.
- **Infectious agents:** Not applicable.

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6. Mechanism / Pathophysiology

Causal chain (upstream → downstream): 1. **Germline heterozygous KDM1A LoF variant** (constitutional; every cell). *(GO: histone H3K4 demethylase activity GO:0032453; H3K9 demethylase GO:0032454; chromatin organization GO:0006325.)* 2. **Somatic loss of wild-type KDM1A allele (1p LOH)** in an adrenocortical clone → complete loss of KDM1A/LSD1 protein (P 34906447). *(Two-hit tumor suppressor; GO:0045596 negative regulation of cell differentiation, GO:0008285/0008284 regulation of cell proliferation.)* 3. **Ectopic expression of the non-mutated GIPR** in adrenocortical cells (aberrant chromatin de-repression) (P 36857084 P 39059410). *(GO:0004930 G-protein coupled receptor activity; CHEBI: glucose-dependent insulinotropic polypeptide.)* 4. **Post-prandial GIP** (secreted by intestinal K cells; CL:0002097 type K enteroendocrine cell) binds adrenal GIPR → **Gs/cAMP/PKA activation** (GO:0071377 cellular response to glucagon-family peptide; GO:0007189 adenylate cyclase-activating GPCR signaling; cAMP CHEBI:17489). 5. **Stimulation of steroidogenesis** (StAR, CYP11A1, CYP11B1) → **meal-**

induced cortisol (CHEBI:17650) hypersecretion and adrenocortical cell proliferation. 6. **Chronic ACTH-independent hypercortisolism** → Cushing syndrome; cortisol feedback suppresses pituitary ACTH (→ low ACTH; internodular adrenal cortex may atrophy).

- **Molecular pathways:** cAMP/PKA signaling (central); GPCR signaling; chromatin/epigenetic regulation (LSD1); Wnt/β-catenin (LSD1 stabilizes β-catenin, (P 38321961) and Notch (P 38152966) as LSD1-regulated proliferation/fate pathways. Reactome: GPCR/adenylate cyclase; KEGG: cortisol synthesis and secretion (hsa04927), cAMP signaling (hsa04024).
- **Cellular processes:** Adrenocortical cell proliferation (nodule formation), dysregulated steroidogenesis, epigenetic transcriptional de-repression.
- **Protein dysfunction: Loss of function** of LSD1 (loss of demethylase + scaffolding activity); **gain of aberrant signaling** through ectopic (structurally normal) GIPR.
- **Metabolic changes:** Secondary cortisol-driven metabolic syndrome — hyperglycemia/insulin resistance (type 2 diabetes), dyslipidemia, central adiposity, protein catabolism (myopathy), bone loss.
- **Immune involvement:** No primary autoimmunity; chronic cortisol excess is immunosuppressive (increased infection risk) — downstream, not causal.
- **Tissue-damage mechanisms:** Systemic glucocorticoid toxicity (vascular, bone, muscle, metabolic) rather than direct adrenal tissue injury.
- **Biochemical abnormality:** Receptor dysfunction (ectopic GIPR coupling meals to steroidogenesis) is the core defect.
- **Molecular profiling:** RNA-seq/exome/SNP-array/methylome/miRNome multiomics defined the FDCS group with GIPR ectopic expression and KDM1A loss (P 34906447); functional validation in the **H295R** human adrenocortical cell line (P 34655521).

7. Anatomical Structures Affected

- **Organ level (primary): Adrenal glands / adrenal cortex** — bilateral (UBERON:0002369 adrenal gland; UBERON:0001235 adrenal cortex). Lateralization: **bilateral**, often asymmetric nodularity.
- **Secondary organ involvement (from cortisol excess):** cardiovascular system (hypertension), pancreas/metabolic (diabetes), skeleton (osteoporosis/fractures), skeletal muscle (myopathy), skin (striae), CNS (neuropsychiatric). Body system: **endocrine** (primary), with cardiovascular, musculoskeletal, integumentary, and metabolic secondary involvement.
- **Tissue / cell level:** Adrenocortical epithelial/steroidogenic cells — **CL:0000538 (adrenal cortex cell)** / zona fasciculata cells; ectopic GIPR on these cells. Trigger cells: intestinal **K cells (CL:0002097)** secreting GIP.
- **Subcellular level:** Nucleus/chromatin (LSD1 site of action; GO:0000785 chromatin; GO:0005634 nucleus); plasma membrane (GIPR; GO:0005886); mitochondria and smooth ER (steroidogenesis; GO:0005739, GO:0005790).
- **Localization:** UBERON:0002369 (adrenal gland), UBERON:0001235 (adrenal cortex); bilateral.

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8. Temporal Development

- **Onset:** Adult-onset (typically 40s–60s), **insidious/chronic**. Because a somatic second hit is required, clinical disease emerges in adulthood despite constitutional carriage.
- **Progression:** Slowly **progressive**; ranges from nonfunctional/mild autonomous cortisol secretion (MACS) to overt Cushing over years; adrenal mass/nodularity increases over time. Not staged formally (benign hyperplasia, not a malignancy staging system).
- **Duration/course:** Chronic, lifelong until surgically treated.
- **Patterns:** Post-prandial **episodic** cortisol surges superimposed on chronic excess; **treatment-induced remission** after adrenalectomy; no spontaneous remission. **Critical intervention window:** early detection in mutation-carrying relatives (cascade screening) before overt Cushing/metabolic damage.

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9. Inheritance and Population

- **Epidemiology:** AIMAH3 is very rare. PBMAH itself is an uncommon cause of overt Cushing but a more frequent cause of bilateral adrenal incidentalomas (41864332); PBMAH is found in ~1/3 of adrenal-incidentaloma patients with subclinical hypercortisolism (35597729). **KDM1A explains ~3.3% of PBMAH index cases** (10/301) and **~90% of FDCS** (39921449). 34906447 Precise population prevalence/incidence figures are not established (data gap).
- **Inheritance: Autosomal dominant** predisposition (germline heterozygous LoF) with a required somatic second hit → **incomplete/variable penetrance** and variable expressivity. No genetic anticipation or repeat expansion. Founder effects/consanguinity not established. Germline mosaicism not specifically documented.
- **Carrier frequency:** Not established; germline KDM1A LoF is rare in gnomAD.
- **Population demographics: Striking female predominance — 100% of KDM1A carriers were women** in the largest cohort (vs ~65% ARMC5, ~67% wild-type; P=.0337) (39921449). No specific ethnic/geographic clustering established; cases reported across Europe, Canada, Brazil, and Asia.

10. Diagnostics

- **Laboratory tests / biomarkers:**
- ACTH-independent hypercortisolism: **suppressed/low ACTH** (HP:0002920), elevated **24h urinary free cortisol** (3.0× ULN typical; 39921449),

loss of diurnal rhythm, **non-suppression on 1-mg overnight and low/high-dose dexamethasone** tests.

- **Inverted rhythm:** low morning, high midnight/post-prandial cortisol. **Morning/midnight plasma cortisol ratio < 0.65 = 100% sensitivity and 100% specificity for FDCS** (P 39921449).
- **Functional confirmatory test: Mixed-meal test** showing a significant post-prandial cortisol rise; cortisol rises after **oral but not IV glucose** (P 21264796).

Screening for aberrant hormone receptors (posture, GnRH, glucagon, vasopressin) per Lacroix protocol may reveal multiple aberrant responses.

- **Imaging:** Adrenal **CT/MRI** shows **bilateral macronodular adrenal hyperplasia** (nodules >1 cm, enlarged glands). ^{18}F-FDG/other functional imaging not required.
- **Histopathology:** Bilateral macronodular adrenocortical hyperplasia; immunohistochemistry can demonstrate **ectopic GIPR** and loss of KDM1A protein in nodules (P 34906447).
- **Genetic testing:** Recommended approach — **germline sequencing of *KDM1A and ARMC5*** for PBMAH patients and families (P 34906447 : "Genetic screening for ARMC5 and KDM1A can now be offered for most PBMAH operated patients and their families"). WES/targeted NGS panels for adrenal tumorigenesis genes are used (P 41113712).

Somatic 1p LOH can be confirmed on tumor DNA (SNP array/CMA). Single-gene KDM1A testing indicated when FDCS biochemistry is present.

- **Clinical criteria / differential diagnosis:** Diagnose per Endocrine Society/ESE hypercortisolism guidelines, then localize to ACTH-independent bilateral adrenal disease. **Differential:** ARMC5-PBMAH (AIMAH2; no food dependence), unilateral GIP-dependent adenoma (19q13.32; unilateral), other aberrant-receptor AIMAH (LH/hCG, β-adrenergic, vasopressin, serotonin), PPNAD/Carney complex (PRKAR1A), McCune-Albright (GNAS), cortisol-producing adenoma, and adrenocortical carcinoma.

- **Screening: Cascade genetic screening** of first-degree relatives of KDM1A carriers; biochemical screening (morning/midnight cortisol ratio, mixed-meal test) in carriers.

11. Outcome / Prognosis

- **Survival/mortality:** AIMAH3 is a **benign** hyperplasia; prognosis is driven by **cortisol-excess complications**, not by malignancy. With treatment (adrenalectomy), hypercortisolism resolves and prognosis is good. Untreated chronic Cushing carries excess cardiovascular/metabolic/infectious mortality. No AIMAH3-specific survival statistics (data gap).
- **Morbidity/function:** Hypertension, type 2 diabetes, osteoporosis/fractures, myopathy, obesity, thromboembolic and infection risk, and neuropsychiatric morbidity — reversible in part after cure.
- **Complications:** Metabolic syndrome, cardiovascular disease, fragility fractures, infections; post-bilateral-adrenalectomy adrenal insufficiency requiring lifelong replacement.
- **Recovery:** Marked clinical/metabolic improvement after adrenalectomy (P 21264796).
- **Prognostic factors/biomarkers:** Degree of hypercortisolism (24h UFC), presence of overt vs mild Cushing, nodule/adenomatous mass, and comorbidity burden. Genotype (KDM1A) predicts the FDCS phenotype and higher UFC (P 39921449).

12. Treatment

- **Surgical (mainstay; NCIT: Adrenalectomy C51765):**
- **Bilateral adrenalectomy** — definitive for overt Cushing; achieves remission; requires **lifelong glucocorticoid + mineralocorticoid replacement**.
- **Unilateral (total/subtotal/partial) adrenalectomy** of the more nodular gland — controls milder disease while preserving some adrenal function; effective in ARMC5-PBMAH and applicable to bilateral disease.

- **Pharmacotherapy:**
- **Somatostatin analogues** (octreotide, octreotide-LAR; multi-ligand **pasireotide/SOM230**) — acutely abolish meal-induced cortisol but show **tachyphylaxis/escape within months** with no durable benefit
(P 21264796). P 23425648
NCIT: Octreotide C1214; Pasireotide C79861.
- **Steroidogenesis inhibitors** (ketoconazole, metyrapone, osilodrostat, mitotane; NCIT: Ketoconazole C599, Metyrapone C61890, Osilodrostat C124087) — symptomatic control of hypercortisolism (general Cushing management).
- **GIPR-targeted therapy (investigational/rational):** GIP-receptor antagonism directly addresses the ectopic-receptor mechanism but is not yet an established therapy.
- **Advanced therapeutics:** No approved gene/cell/RNA therapy. LSD1 inhibitors exist in oncology (e.g., iadademstat; P 40938473)
but are **not** indicated here (the defect is LSD1 loss, so inhibition would be counterproductive).
- **Pharmacogenomics:** None specific to AIMAH3.
- **Treatment strategy / personalized medicine:** Genotype-guided — confirming FDCS/KDM1A supports a mechanism-based approach (meal-timing awareness, consideration of GIP-axis targeting) and, importantly, **family cascade testing**. Choice between unilateral vs bilateral adrenalectomy is individualized to disease severity.
- **Experimental trials:** No AIMAH3-specific registered trials identified; management follows PBMAH/Cushing frameworks (2023 ESE guidelines context, P 41871980).

13. Prevention

- **Primary prevention:** Not possible for the germline lesion. **Secondary prevention** is key: **cascade genetic screening** of relatives of KDM1A carriers and **biochemical surveillance**

(morning/midnight cortisol ratio, mixed-meal test, adrenal imaging) to detect disease early before metabolic damage.

- **Tertiary prevention:** Aggressive management of hypertension, diabetes, osteoporosis, and thrombosis risk; adrenalectomy to prevent complications; post-surgical steroid replacement and sick-day rules to prevent adrenal crisis.
- **Genetic counseling:** Autosomal-dominant predisposition with incomplete penetrance; offer counseling regarding ~50% transmission of the germline allele and variable expression; prenatal/PGT is technically possible but rarely pursued for an adult-onset, treatable, benign condition.
- **Immunization/public-health/environmental:** Not applicable.

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14. Other Species / Natural Disease

- **Taxonomy / orthologs:** Human *KDM1A* (NCBI Gene 23028). Orthologs: mouse *Kdm1a* (NCBI Gene 99982), rat *Kdm1a*, and conserved across vertebrates; LSD1 is highly evolutionarily conserved (present in plants, yeast SWM3/orthologs, Drosophila **Su(var)3-3**, C. elegans **spr-5**).
- **Natural disease in animals:** No naturally occurring KDM1A-driven food-dependent Cushing syndrome is documented in companion animals or wildlife (data gap). (Canine Cushing is usually pituitary-dependent or due to adrenal tumors; no GIP-dependent KDM1A analog reported.)
- **Comparative biology:** LSD1's developmental/epigenetic role is conserved; disease-specific adrenal mechanism appears human-observed. Zoonotic potential: not applicable.

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15. Model Organisms

- **Cellular / in vitro models: H295R** human adrenocortical carcinoma cell line used to functionally validate GIPR-driven cortisol secretion and the effect of KDM1A defects (P 34655521). P 34906447

Patient-derived adrenal tissue used for RNA-seq/methylome/IHC
(P 34906447).
iPSC/organoid adrenal models are emerging but not yet AIMAH3-specific.

- **Mouse models: *Kdm1a* knockout mice** are established for developmental studies (e.g., conditional Kdm1a deletion in nephron progenitors causing glomerulosclerosis/cysts, P 41797715 ; ESC studies P 39237615).
  Complete germline Kdm1a knockout is embryonic-lethal (LSD1 essential for embryogenesis), so no constitutive-null adult model exists; a **conditional/adrenal-specific Kdm1a knockout with somatic loss** would be required to model AIMAH3 — **not yet reported** (data/model gap).
- **Genetic model types available:** Knockout, conditional (floxed), tissue-specific Cre lines for *Kdm1a*; CRISPR/Cas9 KDM1A deletion in human organoids
  (P 41797715).
- **Phenotype recapitulation:** Existing Kdm1a models capture LSD1's epigenetic/developmental functions but **do not recapitulate the adrenal FDCS phenotype** (no ectopic GIPR / food-dependent cortisol model published). This is a key limitation and research opportunity.
- **Resources:** MGI (*Kdm1a*), IMPC/IMSR for knockout alleles; Cellosaurus (H295R, CVCL_0459).

Supported vs Refuted Hypotheses

Supported: - AIMAH3 (OMIM #620990) = KDM1A-driven, GIP/food-dependent Cushing syndrome
(P 34906447 P 39921449 P 41864332).
- Two-hit tumor-suppressor mechanism: germline truncating KDM1A LoF + somatic 1p LOH

(P 34906447).
- Ectopic adrenal GIPR couples meals to cortisol via cAMP/PKA (P 39059410). P 36857084
- Morning/midnight cortisol ratio <0.65 diagnoses FDCS with 100% sensitivity/specificity (P 39921449).
- Adrenalectomy definitive; somatostatin analogs only transiently effective (P 21264796). P 23425648
- Striking female predominance (P 39921449).

Refuted / excluded for AIMAH3 specifically: - ARMC5 as the cause (that is AIMAH2/PBMAH1) — ARMC5 carriers do **not** have FDCS (P 39921449).
- 19q13.32 GIPR duplication as the mechanism — that drives **unilateral** GIP-adenomas, not bilateral AIMAH3 (P 36857084).
- LSD1 *inhibitors* as therapy — the lesion is LSD1 *loss*.

Limitations and Future Directions

- Very small patient numbers (tens of KDM1A cases worldwide); no formal prevalence/ incidence, penetrance estimates, survival, or QoL data specific to AIMAH3.
- The mechanism by which KDM1A loss de-represses *GIPR* is not fully resolved; the extreme female predominance is unexplained.
- No animal model reproduces the adrenal FDCS phenotype — an adrenal-specific conditional Kdm1a model is needed.

- GIPR antagonism is a rational but untested targeted therapy.
- Reported (limited-evidence) associations of KDM1A carriers with other tumors (e.g., monoclonal gammopathy/myeloma) warrant confirmation before inclusion in surveillance.

Evidence key PMIDs: 34906447 (Vaczlavik 2022, KDM1A discovery/multiomics), 34655521 (Chasseloup 2021, GIPR/KDM1A cohort + H295R), 39921449 (Bouys 2025, 301-case screening/genotype-phenotype), 39059410 (Bouys & Bertherat 2024, 35-year FDCS review), 36857084 (Lacroix 2023, GIP-dependent CS mechanisms), 41864332 (Chasseloup & Kamenický 2026, review), 21264796 / 23425648 (somatostatin-analog treatment), 35597729 (PBMAH epidemiology), 38152966 / 39237615 / 38321961 / 41797715 (KDM1A/LSD1 biology & models).
