

Congenital Isolated ACTH Deficiency — Comprehensive Disease Characterization

Disease: Congenital Isolated ACTH Deficiency (IAD) **MONDO:** MONDO:0008720 · **Category:** Mendelian (monogenic endocrine disorder) **Report type:** Literature-based knowledge-base compilation (no primary datasets provided) **Evidence base:** 40 primary papers/reviews reviewed across 5 iterations; 8 confirmed findings recorded to the knowledge graph; evidence types indicated per claim (human clinical, model organism, in vitro, computational/structural). Seminal references include the TPIT discovery (Lamolet 2001, *Cell*,

[P 11290323](#)) and the largest clinical series (Couture 2012, [P 22170728](#)).

1. Disease Information

Overview. Congenital Isolated ACTH Deficiency (IAD) is a rare monogenic form of **secondary (central) adrenal insufficiency** characterized by low or undetectable serum cortisol due to deficient pituitary **adrenocorticotrophic hormone (ACTH)** production, with **preservation of all other anterior pituitary hormones** (GH, TSH, LH/FSH, prolactin) and normal pituitary anatomy. The best-defined form is **neonatal-onset, complete IAD** caused by biallelic loss-of-function variants in **TBX19/TPIT** ([P 22170728](#)).

[P 15613420](#)). It is clinically important because, untreated, it can cause **neonatal death from acute adrenal crisis**, yet it is fully treatable with glucocorticoid replacement.

Key identifiers. - **MONDO:** MONDO:0008720 - **OMIM:** #201400 (Adrenocorticotrophic hormone deficiency / isolated ACTH deficiency); gene **TBX19** OMIM 604614 - *Orphanet:* ORPHA 442 (*Isolated ACTH deficiency*) - *ICD-10:* E23.0 (*Hypopituitarism, includes isolated deficiency of*

pituitary hormones); ICD-11: 5A61.0 (Hypofunction of pituitary gland / ACTH deficiency) - MeSH: "Adrenocorticotrophic Hormone" / "Hypopituitarism"; "Adrenal Insufficiency" - Gene (HGNC):* TBX19 (HGNC:11596), alias TPIT; also NFKB2 (HGNC:7795), POMC (HGNC:9201)

Synonyms / alternative names. Isolated ACTH deficiency; IAD; TPIT deficiency; congenital isolated adrenocorticotropin deficiency; isolated adrenocorticotrophic hormone deficiency; isolated corticotropin deficiency.

Information source. Derived predominantly from **aggregated disease-level resources** (OMIM, Orphanet) and **individual-patient case reports/series** (e.g., the 91-patient TPIT series,

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No population EHR datasets were used here.

2. Etiology

Primary cause: genetic (Mendelian). IAD is not infectious or environmentally acquired. The principal molecular cause of neonatal-onset **complete** IAD is **biallelic (homozygous or compound heterozygous) loss-of-function (LOF) in TBX19/TPIT**, a pituitary-restricted T-box transcription factor required for corticotroph terminal differentiation and POMC transcription

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In the largest series, TPIT mutations were found in **65% of neonatal-onset complete IAD** but **0% of partial or late-onset IAD**

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"we found a TPIT mutation in 65% of patients with neonatal-onset complete IAD. These patients are homozygous or compound heterozygous for TPIT mutations, and their parents are healthy heterozygous carriers."

([P 22170728](#))

human clinical)

Genetic risk factors / genetic heterogeneity. Other monogenic causes of congenital/childhood central ACTH deficiency: - **NFKB2** (DAVID syndrome) — heterozygous, usually de novo C-terminal mutations; ACTH deficiency + common variable immunodeficiency

([P 37322808](#))

([P 25524009](#))

- **POMC** — biallelic LOF; adrenal insufficiency with early-onset obesity and red hair (not truly "isolated")

([P 35775692](#))

- Rare/other hypopituitarism genes may present with ACTH deficiency within broader combined pituitary hormone deficiency.

Environmental risk factors. None established as causal for the congenital genetic disease.

Consanguinity increases the chance of homozygous TPIT/POMC LOF (autosomal recessive). Family history of an affected sibling/neonatal death is a major risk indicator.

Protective factors. No genetic or environmental protective modifiers are established. The main "protective" intervention is **presymptomatic diagnosis** (prenatal/cascade testing in at-risk families) enabling immediate glucocorticoid replacement.

Gene–environment interactions. Not applicable as a cause. Clinically, **physiological stressors** (infection, fasting, surgery) unmask/precipitate adrenal crisis on the genetic background of cortisol deficiency — a genotype × stressor interaction at the level of clinical decompensation rather than disease causation.

3. Phenotypes

Neonatal TPIT-related IAD has a **highly homogeneous** presentation (

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Onset is typically within **hours to days** of birth.

Phenotype	Type	HPO term	Onset	Severity	Frequency
Hypoglycemia (recurrent, severe; seizures, limpness, apnea/ respiratory arrest)	Lab + clinical sign	HP:0001943 (Hypoglycemia); HP:0001998 (Neonatal hypoglycemia)	Neonatal	Severe	Very frequent (hallmark)
Low/ undetectable serum cortisol	Lab abnormality	HP:0008163 (Decreased circulating cortisol)	Neonatal	Severe	Near-universal
Inappropriately low/normal plasma ACTH	Lab abnormality	HP:0011736 (Decreased circulating ACTH)	Neonatal	—	Defining feature
Prolonged conjugated (cholestatic) jaundice	Clinical sign / lab	HP:0002908 (Conjugated hyperbilirubinemia); HP:0001396 (Cholestasis)	Neonatal	Moderate–severe	Frequent
Seizures	Clinical sign	HP:0001250 (Seizure)	Neonatal	Severe	Frequent (secondary to hypoglycemia)
Adrenal insufficiency / adrenal crisis	Clinical	HP:0000846 (Adrenal insufficiency)	Neonatal–lifelong	Life-threatening	Core
Hypokalemia / electrolyte disturbance	Lab	HP:0002900 (Hypokalemia)	Neonatal	Variable	Reported
Hyponatremia (dilutional, cortisol-dependent)	Lab	HP:0002902 (Hyponatremia)	Variable	Variable	Reported (esp. later/adult cases)
	Physical		Congenital	Mild	

Phenotype	Type	HPO term	Onset	Severity	Frequency
Facial dysmorphism (long philtrum, depressed nasal root, epicanthus, low-set ears, mild hypertelorism)		HP:0000271 (Abnormal facial shape)			Occasional (reported in some cases)
Prolonged/severe infections, lethargy, poor feeding, failure to thrive	Clinical	HP:0004322/ HP:0001508	Neonatal–infancy	Variable	Variable

- **Severity/progression:** Episodic life-threatening decompensations (hypoglycemia, adrenal crisis) on a chronic lifelong deficiency; metabolic/hepatic features are **fully reversible** on hydrocortisone.
- **Important distinction:** Because ACTH is **low**, there is **no hyperpigmentation** (unlike primary adrenal insufficiency/FGD). No salt-wasting/mineralocorticoid deficiency (aldosterone preserved).
- **Quality-of-life impact:** With treatment, generally normal growth, development and QoL; residual burden stems from chronic medication dependence, risk of adrenal crisis, and the vigilance required for sick-day management (QoL instruments: AddiQoL, SF-36, EQ-5D — disease-specific data limited).

Evidence:

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(homogeneous presentation), 15301051 (hypoglycemia + conjugated hyperbilirubinemia resolving on hydrocortisone), 34564059 (neonatal onset at 15 h, undetectable cortisol with normal-range ACTH), 40990269 (hypoglycemic seizures, hypokalemia, cholestasis, dysmorphism).

4. Genetic / Molecular Information

Causal gene (principal): **TBX19 / TPIT** — HGNC:11596; OMIM 604614; locus 1q24.2; *T-box transcription factor family. Encodes a corticotroph/melanotroph-restricted DNA-binding transcription factor. TPIT was discovered by Lamolet et al. (2001, Cell;*

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as a T-box factor present only in pituitary POMC lineages (corticotrophs, melanotrophs) and "apparently in no other tissue, including hypothalamic POMC neurons," that activates POMC transcription cooperatively with PITX1 and can initiate POMC-lineage differentiation; the same study reported TPIT mutations in patients with isolated POMC-derived ACTH deficiency.*

Other causal genes: **NFKB2** (HGNC:7795; 10q24.32; DAVID syndrome), **POMC** (HGNC:9201; 2p23.3; adrenal insufficiency–obesity–red hair).

Pathogenic variant spectrum (TBX19). All variant classes reported, all **loss-of-function**: - **Missense** (e.g., p.Met86Arg within the T-box, disrupting protein–protein interaction/DNA binding;

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- **Nonsense** (e.g., p.Arg286Ter;

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- **Frameshift** / **small indels** (e.g., c.782delA;

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- **Splice-site and synonymous/exonic splice-disrupting** (e.g., p.Thr96= c.288G>A causing missplicing; exon-2

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- **Large deletions**

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Functional consequences / **mechanisms of LOF**

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nonsense-mediated mRNA decay, aberrant splicing, loss of DNA binding, and loss of protein–

protein interactions (e.g., with PITX1 and coactivator SRC2). The M86R mutation impairs cooperative DNA binding (homodimers, PITX1 heterodimers) and SRC2 recruitment despite retaining monomeric DNA binding

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 in vitro).

Variant classification (ACMG/AMP). Reported variants are predominantly **pathogenic/likely pathogenic** (functional assays + recessive segregation + absent/rare in population databases). Allele frequencies are very low in **gnomAD** (e.g., rs376493164 $\sim 1 \times 10^{-5}$, no homozygotes;

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Origin: **germline**, biallelic (AR) for TBX19/POMC; heterozygous (often **de novo**) for NFKB2. No somatic involvement.

Modifier genes. None established. Partners/functionally related factors (PITX1, NEUROD1, PAX7, ETV1, CREB3L2, NR4A/Nur family) shape the corticotroph program but are not reported disease modifiers in IAD

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Epigenetics. No disease-specific methylation signature established in patients. Mechanistically, the POMC locus is controlled by pioneer-factor chromatin remodeling (PAX7) and lineage enhancers on which TPIT acts

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— relevant to normal regulation rather than a documented epigenetic lesion in IAD.

Chromosomal abnormalities. Not characteristic; large TBX19 deletions occur but gross cytogenetic abnormalities are not a feature.

5. Environmental Information

- **Environmental/toxic factors:** None causal for congenital IAD.
- **Infectious agents:** None causal. Intercurrent **infection** is the most common **precipitant of adrenal crisis** (not a cause of the disease).
- **Lifestyle factors:** Not applicable to disease causation. Relevant to management: adherence, stress-dosing behavior, carrying emergency hydrocortisone.

(Note: acquired/late-onset isolated ACTH deficiency in adults can be autoimmune/hypophysitis-related or drug-related, e.g., immune-checkpoint-inhibitor hypophysitis — but that is a separate, non-congenital entity.)

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic LOF variant in TBX19/TPIT** (germline) **results in** absent or non-functional TPIT transcription-factor protein (nucleus). *[demonstrated: functional assays,*

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2. Loss of TPIT **leads to** failure of **terminal differentiation of pituitary corticotrophs** (and melanotrophs) and failure to activate the **POMC** gene via the TPIT/PITX1 regulatory element. *[demonstrated in human + mouse,*

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3. Failed POMC program **results in** absent/deficient **POMC** precursor and its product **ACTH** in anterior-pituitary corticotrophs. *[demonstrated]*

4. Low circulating ACTH **leads to** loss of **MC2R (ACTH receptor) + MRAP1** activation on adrenocortical (zona fasciculata) cells. *[downstream; receptor biology demonstrated,*

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5. Loss of MC2R/cAMP–PKA signaling **results in** failure of **adrenal steroidogenesis → cortisol (glucocorticoid) deficiency**. *[inferred from HPA physiology + clinical cortisol absence]*

6. Cortisol deficiency **leads to** the clinical phenotype — via branches:

7. **6a.** Impaired hepatic gluconeogenesis/glycogenolysis → **neonatal hypoglycemia → seizures/apnea**. *[inferred/clinical]*

8. **6b.** Impaired bile flow/hepatic adaptation → **neonatal cholestasis/conjugated hyperbilirubinemia**. *[clinical association, reversible on replacement]*

9. **6c.** Loss of permissive glucocorticoid effects on vascular tone/stress response → **hypotension, vulnerability to adrenal crisis → potential neonatal death**. *[clinical,*

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10. Because TPIT is **lineage-restricted, other pituitary hormones are spared** → the deficiency is **isolated** (selective ACTH loss). *[demonstrated]*

Branch (NFKB2/DAVID): heterozygous C-terminal NFKB2 mutation → defective non-canonical NF-κB p100→p52 processing → corticotroph dysfunction **and** B-cell/immune defect → ACTH deficiency + hypogammaglobulinemia

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Supporting detail

- **Molecular pathways:** POMC transcriptional regulation (TPIT–PITX1–NEUROD1; NR4A/Nur-mediated CRH response; glucocorticoid-receptor negative feedback)

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downstream **cAMP–PKA** steroidogenic signaling at MC2R

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non-canonical NF- κ B (NFKB2 branch).

- **Cellular processes:** arrest of corticotroph terminal differentiation; TPIT also drives a cell-cycle-control switch and secretory/translational scale-up via **CREB3L2**

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BDNF autocrine loop couples precursor engagement to glucocorticoid feedback

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P 42392084);

- **Protein dysfunction:** TPIT missense (e.g., M86R) → impaired cooperative DNA binding and coactivator (SRC2) recruitment

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Structural note: M86 lies at the T-box dimer interface.

- **Immune involvement:** only in the **NFKB2/DAVID** branch (hypogammaglobulinemia/CVID). TPIT-IAD is **not** immune-mediated.
- **Metabolic changes:** cortisol-dependent failure of gluconeogenesis → hypoglycemia; no primary enzyme defect.

GO terms: GO:0045944 (positive regulation of transcription by RNA Pol II), GO:0003700 (DNA-binding transcription factor activity), GO:0030855/GO:0030154 (epithelial/cell differentiation), GO:0042446 (hormone biosynthetic process), GO:0006704 (glucocorticoid biosynthetic process), GO:0051458 (corticotropin secretion), GO:0007267 (cell–cell signaling). **CL terms:** CL:0000152 (corticotroph / corticotropic cell), CL:1000298? melanotroph (CL:0002487), CL:0000164 (endocrine cell), adrenal cortical cell (CL:0002097 zona fasciculata cell).

7. Anatomical Structures Affected

- **Organ level (primary): Anterior pituitary / adeno****hypophysis** (UBERON:0002196 / anterior pituitary UBERON:0002196; adeno**hypophysis UBERON:0002196) — specifically the corticotroph population. Secondary (functional): Adrenal cortex** (UBERON:0001235), which is hypofunctional/atrophic due to lack of ACTH trophic drive (adrenal hypoplasia in

Tpit-null mice,

P 15525497

- **Body systems: Endocrine system** (hypothalamic–pituitary–adrenal axis); secondary impacts on **hepatobiliary** (cholestasis), **metabolic/CNS** (hypoglycemic seizures), **cardiovascular** (hypotension in crisis). In the NFKB2 branch, the **immune system** is involved.
- **Tissue/cell level:** pituitary **corticotroph** cells (CL:0000152) and melanotrophs (intermediate lobe, vestigial in humans); adrenocortical cells of the **zona fasciculata** (CL:0002097).
- **Subcellular (GO Cellular Component): nucleus** (GO:0005634, site of TPIT action/DNA binding); secretory pathway / dense-core secretory granules for ACTH (GO:0030141); plasma membrane MC2R receptor complex on adrenal cells (GO:0005886).
- **Localization/lateralization:** midline pituitary; bilateral adrenal glands. No lateralization.

8. Temporal Development

- **Onset: Congenital**, typically presenting in the **neonatal period** (first hours to days of life) for TPIT-complete IAD; NFKB2/DAVID typically presents in **childhood** (mean ACTH-deficiency diagnosis ~8.6 y, often after infections/alopecia) (**P** 37322808).
- Onset pattern: **acute** decompensation (hypoglycemia/crisis) superimposed on a congenital deficiency.
- **Progression:** The hormonal deficiency is **stable and lifelong** (not progressive in the TPIT form), but the clinical course is **episodic**, punctuated by stress-precipitated adrenal crises. Metabolic/hepatic features **remit rapidly** with glucocorticoid replacement (treatment-induced remission of manifestations; the underlying deficiency does not remit).
- **Critical periods:** The **neonatal window** is the period of highest vulnerability (risk of death) and of greatest benefit from early diagnosis/replacement. Lifelong vigilance during intercurrent illness/surgery.
- **Duration:** Chronic, lifelong; requires lifelong replacement.

9. Inheritance and Population

- **Epidemiology: Very rare.** Congenital IAD has no robust prevalence/incidence estimates (Orphanet: prevalence unknown/<1/1,000,000 order of magnitude; reported as an "underestimated cause of neonatal death,"

(P 15613420).

The literature consists of case reports and a few multinational series (largest = 91 IAD patients; TPIT mutations in 17/27 then expanded,

(P 15613420).

(P 22170728).

- **Inheritance patterns:**
- **TBX19/TPIT: Autosomal recessive** (homozygous/compound heterozygous; unaffected heterozygous carrier parents)

(P 15613420).

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- **POMC:** autosomal recessive.
- **NFKB2 (DAVID): autosomal dominant**, frequently **de novo**

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- **Penetrance:** For biallelic TPIT LOF, **complete/high penetrance** with early lethal potential if untreated; NFKB2 shows **variable expressivity** (endocrine vs immune features vary within families; some carriers show only immune phenotype)

(P 25524009).

- **Expressivity:** TPIT-IAD is **phenotypically homogeneous**; NFKB2 is **variable**.
- **Genetic anticipation:** Not applicable (no repeat expansion).
- **Germline mosaicism:** Not specifically documented; de novo events occur for NFKB2.
- **Founder effects / consanguinity:** **Consanguinity** contributes to homozygous TPIT cases; a recurrent TPIT mutation was seen in multiple unrelated families

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A **POMC 5'-UTR founder mutation** was described in the Perm Tatar population

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— relevant to the POMC-deficiency differential.

- **Carrier frequency:** Very low; TPIT pathogenic alleles are rare in gnomAD.
- **Demographics / sex ratio:** No strong sex predilection for TPIT-IAD (autosomal). Reported across diverse ethnicities/geographies; no defined endemic region.

10. Diagnostics

Biochemical (first-line). - **Low/undetectable serum cortisol** (e.g., <1 µg/dL; LOINC 2143-6) with **inappropriately low or normal plasma ACTH** (LOINC 2141-0) — the defining combination of **secondary** adrenal insufficiency

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- **Hypoglycemia** (LOINC 2345-7), sometimes hyponatremia/hypokalemia. - **Normal mineralocorticoid axis:** normal/near-normal aldosterone and plasma renin activity (distinguishes from primary AI). - **Dynamic testing:** low-dose/standard **ACTH (Synacthen) stimulation** may show adrenal response if atrophy is not advanced; **insulin tolerance test / CRH test / metyrapone** assess central axis (used cautiously in neonates). ACTH-stimulation can transiently increase cortisol early

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- **Normal other pituitary hormones** (GH, TSH/free T4, gonadotropins, prolactin) confirms "isolated."

Imaging. Pituitary **MRI** is typically **normal** (no structural lesion) in TPIT-IAD — an important feature separating it from structural hypopituitarism.

Genetic testing (confirmatory). - **Approach:** targeted **single-gene (TBX19)** testing in neonatal complete IAD; **gene panels** for adrenal insufficiency/hypopituitarism (TBX19, POMC, NFKB2, and FGD genes MC2R, MRAP, STAR, NNT, TXNRD2) via **NGS/WES**; **WES/WGS** for undiagnosed cases (HaloPlex/NGS arrays used in practice,

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- CMA/karyotype/FISH, mtDNA, repeat-expansion testing are **not** indicated (not a CNV/mitochondrial/repeat disorder).

Clinical criteria / differential diagnosis. - Primary (ACTH-high) adrenal insufficiency: Familial Glucocorticoid Deficiency (MC2R/MRAP/STAR/NNT/TXNRD2) — high ACTH, hyperpigmentation, preserved mineralocorticoid);

(**P** 37352919)

Addison disease; congenital adrenal hyperplasia (elevated 17-OHP/androgens). - **Central causes:** combined pituitary hormone deficiency/panhypopituitarism (multiple deficits, abnormal MRI); **POMC deficiency** (obesity/red hair,

(**P** 35775692)

NFKB2/DAVID (hypogammaglobulinemia, infections, alopecia,

(**P** 37322808)

- **Key discriminator:** the **ACTH level** (low/normal = central IAD; high = primary).

Screening. No population newborn screening exists for IAD; **cascade genetic testing** and, in families with a known variant, **prenatal/preimplantation testing** enable presymptomatic management

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11. Outcome / Prognosis

- **With early diagnosis + glucocorticoid replacement: excellent prognosis** — hypoglycemia and cholestasis resolve, and normal growth/development is achieved

(**P** 15301051)

Long-term follow-up of TPIT cases supports good outcomes on replacement

(**P** 40727905)

- **Without treatment:** potentially **fatal in the neonatal period** from acute adrenal insufficiency; IAD is described as an **underestimated cause of neonatal death**

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- **Principal ongoing risk / mortality driver: adrenal crisis** during intercurrent illness/stress — in adrenal-insufficiency populations, adrenal crisis mortality is **~0.5/100 patient-years** and a leading cause of death

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Rare severe complications include reversible cardiomyopathy during crisis

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- **Morbidity/QoL:** chronic medication dependence, need for emergency preparedness; neurodevelopmental sequelae possible if recurrent severe neonatal hypoglycemia is not prevented.
- **Prognostic factors:** time to diagnosis, prevention of hypoglycemic brain injury, adherence, quality of sick-day/stress-dosing education.

12. Treatment

Pharmacotherapy (mainstay — lifelong hormone replacement). - **Hydrocortisone**, oral, physiological dosing (~8–15 mg/m²/day divided 2–3×; neonates/infants often need individualized dosing) — rapidly reverses hypoglycemia and cholestasis and restores growth

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NCIT: *Hydrocortisone C379; Glucocorticoid C821; Hormone Replacement Therapy C62604*. - **Mineralocorticoid (fludrocortisone) is generally NOT required** — aldosterone is preserved in central/secondary AI (contrast with primary AI). NCIT: *Fludrocortisone C29089*. - **Stress/sick-day dosing:** double–triple oral hydrocortisone during febrile illness; **parenteral (IM/IV) hydrocortisone** for vomiting, severe illness, surgery, or adrenal crisis (emergency kit + medical alert). Structured stress-dosing protocols reduce crises

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- **Emergency adrenal crisis management:** immediate parenteral hydrocortisone, IV dextrose for hypoglycemia, fluids/electrolyte correction.

Advanced/experimental therapeutics. No gene therapy, cell therapy, RNA therapy, or targeted/immunotherapy exists for IAD; treatment is replacement only. Modified-release hydrocortisone formulations (e.g., Plenadren, Chronocort) aim for more physiological cortisol

rhythms

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 — relevant to adrenal insufficiency broadly. In the **NFKB2/DAVID** branch, **immunoglobulin replacement** addresses the immune deficiency
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Surgical/rehabilitative: not applicable (no surgical target). Supportive care = nutrition, infection management, caregiver education.

Pharmacogenomics: none specific to IAD.

Treatment strategy / personalized medicine: genotype-informed (TPIT vs POMC vs NFKB2) management — e.g., add Ig replacement for NFKB2; weight/obesity and pigmentation surveillance for POMC; otherwise identical glucocorticoid-replacement backbone.

13. Prevention

- **Primary prevention:** Not possible for the germline genetic disease. **Genetic counseling** for at-risk (carrier) couples; options include **prenatal diagnosis** and **preimplantation genetic testing** where a familial variant is known (AR recurrence risk 25%)

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- **Secondary prevention (early detection):** Cascade/presymptomatic genetic testing of newborn siblings in affected families permits immediate glucocorticoid prophylaxis and prevents neonatal death/hypoglycemic injury

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No population newborn-screening program currently targets IAD.

- **Tertiary prevention (preventing complications):** structured **adrenal-crisis prevention** — patient/caregiver education, written stress-dosing plans, emergency hydrocortisone injection kits, medical-alert identification; address knowledge gaps that drive preventable crises/deaths

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([P 40214077](#)).

([P 40416465](#)).

- **Immunization / public health / environmental:** standard childhood immunization (reduces infections that precipitate crisis); in NFKB2/DAVID, vaccine responses may be impaired and Ig replacement considered.
- **Counseling:** genetic counseling re: AR inheritance (TPIT/POMC) vs AD/de novo (NFKB2) and recurrence risks.

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** Mouse *Tbx19/Tpit* (NCBI Taxon 10090; MGI ortholog) is the principal comparative model; TPIT and the POMC regulatory program are **evolutionarily conserved** across mammals

([P 26792828](#)).

PAX7 expression in melanotropes is conserved in human and **dog**

([P 23070814](#)).

- **Natural disease in animals:** No well-established spontaneous TPIT-mutation disease analog is documented in companion animals/livestock (OMIA: not a classically catalogued natural animal disease). Canine pituitary biology is referenced comparatively (Cushing's/adenoma context), not as a natural IAD model.
- **Comparative biology:** Mouse *Tpit*-null endocrine phenotype closely mirrors human IAD (reduced ACTH, undetectable corticosterone, adrenal hypoplasia) — strong mechanistic conservation

([P 15525497](#)).

- **Zoonotic potential:** Not applicable (non-infectious genetic disease).

15. Model Organisms

- **Mouse (*Mus musculus*, NCBI Taxon 10090):**
- **Tpit-null (knockout)** — recapitulates IAD: "*plasma ACTH is greatly reduced ... plasma corticosterone is undetectable and the adrenals are hypoplastic*"
([P 15525497](#)),
model organism). Demonstrates Tpit as positive regulator of POMC-cell differentiation and negative regulator of alternate (gonadotroph) fate.
- **Pax7 knockout** — defines chromatin/enhancer context of Tpit action (melanotrope identity)
([P 23070814](#)).
- **POMC-knockout and adrenalectomized mice** — reveal compensatory corticotrope-precursor accumulation and BDNF/Tpit precursor biology
([P 42392084](#)).
- Resources: **MGI/IMPC/IMSR.**
- **In vitro / cellular: AtT-20** corticotroph tumor cell line (POMC/Tpit functional assays,
([P 21622576](#));
heterologous expression systems for TPIT mutation functional testing and splicing assays
([P 17652218](#));
([P 34564059](#))).
- **Human iPSC-derived pituitary organoids:** model corticotroph deficiency and support the functional role of **NFKB2** in DAVID syndrome
([P 39607428](#)),
in vitro human).
- **Phenotype recapitulation:** strong for the **endocrine core** (ACTH/corticosterone deficiency, adrenal hypoplasia). **Limitations:** neonatal **cholestasis**, dysmorphism, and human-specific developmental/clinical features are not fully modeled; mouse intermediate-lobe (melanotrope) biology differs from humans.

- **Applications:** dissecting corticotroph differentiation, POMC transcriptional control, testing differentiation signals (BDNF, CREB3L2), and modeling genotype-specific mechanisms.

Supported vs. Refuted Hypotheses

Supported: - Biallelic TBX19/TPIT LOF is the principal cause of neonatal-onset **complete** IAD (65% of such cases) —

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- Highly homogeneous neonatal phenotype (hypoglycemia, cholestasis, undetectable cortisol with low/normal ACTH), fatal if untreated, reversible with hydrocortisone —

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- Mechanistic chain TPIT→POMC/ACTH→MC2R→cortisol, with isolated (lineage-restricted) deficiency —

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- Tpit-null mouse recapitulates the endocrine phenotype —

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Refuted / bounded: - TPIT mutations do **NOT** explain **partial** or **late-onset** IAD (0% in those groups) —

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implies additional, partly unknown genetic/acquired causes. - IAD is **not** a mineralocorticoid-deficient, hyperpigmented, or ACTH-high disorder — these features indicate **primary** AI/FGD instead —

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Limitations & Future Directions

- No large-scale prevalence/incidence or registry data; epidemiology is case-series-based.
 - Genetic cause of partial/late-onset IAD remains largely unexplained (gene-discovery opportunity via WES/WGS).
 - Limited QoL and long-term neurodevelopmental outcome data specific to IAD.
 - Mechanistic links from cortisol deficiency to neonatal **cholestasis** remain incompletely defined (largely inferred/clinical).
 - No disease-modifying/curative therapy; replacement is lifelong — future directions include physiological cortisol delivery and, speculatively, corticotroph cell/gene-based restoration.
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Ontology quick-reference

- **Disease:** MONDO:0008720; OMIM #201400; ORPHA:442; ICD-10 E23.0
 - **Genes:** TBX19 (HGNC:11596, OMIM *604614), NFKB2 (HGNC:7795), POMC (HGNC:9201)
 - **HPO:** HP:0001943, HP:0001998, HP:0008163, HP:0011736, HP:0001396, HP:0002908, HP:0000846, HP:0001250, HP:0002900
 - **GO:** GO:0045944, GO:0003700, GO:0030154, GO:0006704, GO:0051458
 - **CL:** CL:0000152 (corticotroph), CL:0002097 (zona fasciculata cell)
 - **UBERON:** UBERON:0002196 (adenohypophysis/anterior pituitary), UBERON:0001235 (adrenal cortex)
 - **CHEBI:** CHEBI:17650 (cortisol), CHEBI:3650 (ACTH), CHEBI:17754 (glucocorticoid class)
 - **NCIT:** C379 (Hydrocortisone), C821 (Glucocorticoid), C62604 (Hormone Replacement Therapy)
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