

Familial Erythrocytosis 4 (ECYT4): A Comprehensive Disease Characteristics Report

Disease: Familial Erythrocytosis 4 (ECYT4) **MONDO ID:** MONDO:0012729 | **OMIM:** 611783 | **Gene:** *EPAS1* (*HIF2A*) **Category:** Mendelian, autosomal dominant **Report date:** 2026-10-14

Summary

Familial Erythrocytosis 4 (ECYT4) is a rare autosomal dominant, secondary (erythropoietin-driven) hereditary erythrocytosis caused by germline gain-of-function missense variants in *EPAS1* (which encodes hypoxia-inducible factor 2-alpha, HIF-2 α). The causal variants cluster in the oxygen-dependent degradation domain (ODDD) of HIF-2 α near the critical hydroxylation target proline 531 (P531). By disrupting this hydroxylation site, the variants prevent prolyl hydroxylase domain protein 2 (PHD2/EGLN1) from tagging HIF-2 α for von Hippel–Lindau (pVHL)-mediated proteasomal degradation. HIF-2 α is consequently stabilized, accumulates, translocates to the nucleus, and constitutively transactivates its target gene *EPO*, producing inappropriate erythropoietin secretion and absolute erythrocytosis with an inappropriately normal-to-elevated serum EPO level.

ECYT4 sits within a well-defined nosology of four Mendelian familial erythrocytoses. It is distinguished from ECYT1 (*EPOR*, primary, low EPO), ECYT2 (*VHL*/Chuvash, recessive, oxygen-sensing), and ECYT3 (*EGLN1*/PHD2, oxygen-sensing) as the *EPAS1*/HIF2A, high-EPO, dominantly inherited oxygen-sensing subtype. The same molecular lesion, when it arises post-zygotically as somatic mosaicism, produces a distinct multisystem disorder — **Pacak–Zhuang syndrome (PZS)** — characterized by multiple paragangliomas/pheochromocytomas, duodenal somatostatinomas, and polycythemia, along with ocular/retinal vascular abnormalities, pancreatic neuroendocrine tumors, and other developmental anomalies. ECYT4 (germline, heritable) and PZS (mosaic, tumor-predisposing) are therefore two phenotypic expressions of the same gain-of-function biology.

Clinically, ECT4 is managed supportively with therapeutic phlebotomy, cardiovascular-risk optimization, and low-dose aspirin, while cytoreductive therapy is avoided. The most important recent advance is mechanism-targeted pharmacotherapy: **belzutifan**, a small-molecule HIF-2 α inhibitor, has been used successfully to normalize hemoglobin in germline *EPAS1*-associated polycythemia without further phlebotomy, directly correcting the underlying pathophysiology. This report integrates nine confirmed findings drawn from 15 primary papers to document the disease across all requested domains, flagging gaps where disease-specific data are absent.

Key Findings

Finding 1 — Causal genetics: germline gain-of-function *EPAS1*/HIF2A variants clustering near Pro531

ECT4 is caused by heterozygous germline gain-of-function missense variants in *EPAS1*, the gene encoding HIF-2 α . In a European cohort of 41 patients plus 28 relatives with *EPAS1*-associated erythrocytosis, 11 mutations were classified as pathogenic across 17 patients and 23 relatives, and four novel mutations — **D525G, L526F, G527K, and A530S** — were identified clustering close to the key proline residue P531. The functional impact of these variants was validated by luciferase reporter assays demonstrating enhanced HIF-2 α -dependent *EPO* promoter induction. As the authors state, *"Gain-of-function mutations in the EPAS1/HIF2A gene have been identified in patients with hereditary erythrocytosis that can be associated with the development of paraganglioma, pheochromocytoma and somatostatinoma"* and *"We described four new mutations (D525G, L526F, G527K, A530S) close to the key proline P531, which broadens the spectrum of mutations involved in erythrocytosis"* ([PMID: 36700397](#)).

The P531 residue is the primary hydroxylation acceptor within the ODDD; variants adjacent to it mechanically shield the hydroxylation machinery, which explains the tight genotypic clustering. **Variant class:** missense (point mutations). **Origin:** germline (heritable). **Functional consequence:** gain of function. **HGNC:** EPAS1.

Finding 2 — Core mechanism: escape from PHD2 hydroxylation and VHL degradation stabilizes HIF-2 α and drives EPO

Under normoxia, HIF- α subunits are hydroxylated on specific proline residues by PHD2 (EGLN1), which creates the recognition motif for the pVHL E3 ubiquitin ligase complex and targets HIF- α for proteasomal degradation. Congenital erythrocytosis arises from lesions anywhere along this oxygen-sensing axis: *"CE has been found to be caused by loss-of-function mutations in VHL and PHD2/EGLN1 as well as gain-of-function mutations in HIF-2 α (EPAS1), all resulting in constitutive activation of EPO signaling"* (PMID: 33840141).

In ECYT4 specifically, the gain-of-function variants cause HIF-2 α to evade hydroxylation: *"HIF-2 α evades steady-state hydroxylation by the prolyl hydroxylase type 2 (PHD2), which accelerates von Hippel-Lindau (VHL)-mediated proteasomal degradation. In this situation, HIF-2 α is stabilized and can translocate to the nucleus"* (PMID: 39426935). Stabilized nuclear HIF-2 α dimerizes with HIF-1 β (ARNT) and transactivates hypoxia-response genes, foremost among them *EPO*. This is the central, biochemically demonstrated causal step of the disease.

Finding 3 — HIF-2 α is the principal physiologic transcriptional driver of EPO, tuned by oxygen, iron, and 2-oxoglutarate

The reason *EPAS1* gain-of-function produces erythrocytosis is that HIF-2 α is the dominant physiologic transactivator of *EPO*: *"Hypoxia-inducible factor-2 alpha (HIF-2 α), a positive regulator of the EPO gene"* (PMID: 28263291). HIF-2 α activity is normally tuned by multiple inputs — molecular oxygen and 2-oxoglutarate (co-substrates of PHD2), and iron, which modulates both PHD2 activity and HIF-2 α translation. *EPO* expression and renal HIF-2 α are suppressed by iron through an oxidative-stress-dependent pathway, and erythropoietin production is modulated by iron via iron-regulatory-protein/iron-responsive-element control of HIF-2 α (PMID: 28263291; PMID: 35618957). In ECYT4, the constitutive stabilization of HIF-2 α overrides these physiologic brakes, uncoupling *EPO* production from true tissue oxygenation.

Finding 4 — Historical discovery and heritability

EPAS1/HIF2A gain-of-function mutations were first reported in 2012. The landmark paper identified *"two novel somatic gain-of-function mutations in the gene encoding hypoxia-inducible factor 2 α (HIF2A) in two patients, one presenting with paraganglioma and the other with paraganglioma and somatostatinoma, both of whom had polycythemia. The two mutations were associated with increased HIF-2 α activity and increased protein half-life"* (PMID: 22931260). The heritable, germline nature of the erythrocytosis phenotype was established shortly afterward

by the report of a germline **F374Y (exon 9)** variant: *"We now report a polycythemic patient with a novel germline HIF2A (F374Y) (exon 9) mutation, inherited from his mother, who developed PHEO/PGL. We show that this is a gain-of-function mutation"* (PMID: 23090011). Notably, there was no loss of heterozygosity in the tumor, consistent with a dominant gain-of-function rather than a classic tumor-suppressor two-hit mechanism.

Finding 5 — The mosaic counterpart: Pacak–Zhuang syndrome

The somatic-mosaic version of ECYT4 biology is Pacak–Zhuang syndrome (PZS): *"a new syndrome of multiple paragangliomas, somatostatinomas, and polycythemia caused by early postzygotic mosaic mutations in EPAS1, encoding hypoxia-inducible factor 2 alpha (HIF-2α)"* (PMID: 37450881). In PZS, polycythemia precedes tumor development and is only partially corrected by tumor removal, with recurrence shortly after surgery (PMID: 31091718). EPAS1-related pheochromocytomas/paragangliomas (PPGLs) comprise roughly 3–6% of all PPGLs and show a characteristic phenotype: *"EPAS1-related PPGLs usually occur in the second or third decade of life, more frequently in females, and are usually multiple, adrenal and extra-adrenal, and norepinephrine-secreting"* with metastatic disease in up to 30% (PMID: 39426935). The phenotypic spectrum also includes ocular/retinal and choroidal vascular abnormalities (PMID: 31876943), Chiari malformation type 1 (PMID: 31185588), and pancreatic neuroendocrine tumors (PMID: 41518596).

Finding 6 — Mechanism-targeted therapy: belzutifan

The most consequential therapeutic advance is direct pharmacologic inhibition of HIF-2α. In the first reported use of belzutifan for germline EPAS1-associated polycythemia — an 11-year-old with a likely-pathogenic EPAS1 variant causing polycythemia, pulmonary hypertension, and ischemic stroke — *"she started novel therapy with belzutifan, a small molecule inhibitor of HIF-2α, to target her underlying disease pathophysiology. This is the first reported usage of belzutifan for EPAS1-associated polycythemia. The therapy has been well tolerated, and her hemoglobin was restored to normal levels without the need for additional phlebotomy"* (PMID: 40879399). This addresses the disease at its causal node rather than merely managing its hematologic consequence.

Finding 7 — Transgenic mouse model recapitulation

A transgenic mouse model expressing a gain-of-function EPAS1/HIF-2α mutation recapitulates the human phenotype. Through the NIH PPGL translational program, *"the generation and study of a corresponding disease mouse model ... has provided new insights into the natural history of*

these developmental anomalies and the pathophysiologic role of HIF-2 α " (PMID: 37450881). A specific **Epas1**^{A529V} transgenic model reproduced the ocular/retinal and choroidal vascular features seen in patients (PMID: 31876943), and models have been used to study polycythemia, vascular malformations, and neural tube defects (PMID: 31091718).

Finding 8 — Diagnostic framework

Diagnosis requires systematic exclusion of polycythemia vera (PV) and secondary causes. In JAK2-unmutated erythrocytosis, *"Hereditary erythrocytosis should be considered in longstanding erythrocytosis with a positive family history; causes include EPOR mutations (subnormal Epo), high oxygen affinity hemoglobin variants, PIEZO1 mutations, 2,3-bisphosphoglycerate deficiency, methemoglobinemia, and germline oxygen sensing pathway mutations (HIF2A-PHD2-VHL)"* (PMID: 41123216). Management guidance: *"Cytoreductive therapy should be avoided. Phlebotomy should be considered for symptom control. Cardiovascular risk optimization and low-dose aspirin are advised, while the role of HIF2A inhibitors remains unclear"* (PMID: 41123216).

Finding 9 — Position within the Mendelian erythrocytosis nosology

ECYT4 is one of four classically numbered familial erythrocytoses, distinguished by causal gene, inheritance, and EPO level (see table in the Mechanistic Model section). It is the *EPAS1*/HIF2A, high-EPO, autosomal-dominant, oxygen-sensing subtype (PMID: 33840141).

Section-by-Section Report

1. Disease Information

- **Overview:** ECYT4 is a rare inherited absolute erythrocytosis (increased red cell mass) caused by constitutive activation of HIF-2 α , leading to inappropriate erythropoietin production and secondary polycythemia. It is a lifelong, congenital-onset condition.
- **Key identifiers:** MONDO:0012729; OMIM 611783; gene *EPAS1* (HGNC:3374, OMIM 603349, chromosome 2p21). MeSH: "Familial Erythrocytosis" / "Polycythemia." ICD-10: D75.1 (secondary polycythemia). ICD-11: 3A81 (secondary polycythaemia). Orphanet: within the familial erythrocytosis grouping (e.g., ORPHA:90042 "Autosomal dominant secondary polycythemia"). (Exact Orphanet subtype code for ECYT4 is not firmly established in the reviewed sources — flagged as uncertain.)

- **Synonyms/alternative names:** Familial erythrocytosis 4; ECYT4; erythrocytosis, familial, 4; *EPAS1*-related/HIF2A-related congenital erythrocytosis; HIF2A erythrocytosis. The germline erythrocytosis-only presentation is distinct from the mosaic "Pacak–Zhuang syndrome" / "EPAS1 gain-of-function mutation syndrome."
- **Information source:** Primarily aggregated disease-level resources (OMIM, cohort studies, case series) complemented by individual case reports; no large EHR-derived datasets were used.

2. Etiology

- **Primary cause (genetic):** Germline heterozygous gain-of-function missense variants in *EPAS1*/HIF2A (PMID: 36700397; PMID: 23090011).
- **Genetic risk factors:** The causal variants themselves are the risk factor; they cluster in the C-terminal ODDD near codon 531 (e.g., D525G, L526F, G527K, A530S) and in exon 9 (e.g., F374Y). No separate susceptibility loci or validated modifier genes are established for ECYT4 in the reviewed literature.
- **Environmental risk factors:** None established as *causing* ECYT4. However, HIF-2 α activity is physiologically sensitive to hypoxia and iron; environmental hypoxia (altitude) and iron status may plausibly modulate phenotype severity (inferred, not demonstrated for ECYT4).
- **Protective factors:** No genetic protective variants or environmental protective factors specific to ECYT4 are documented. Mechanistically, iron sufficiency suppresses HIF-2 α /EPO (PMID: 28263291), but therapeutic phlebotomy deliberately induces iron deficiency, so the net clinical interaction is complex (inferred).
- **Gene–environment interactions:** Not specifically characterized; the oxygen- and iron-responsiveness of the HIF pathway is the plausible substrate for GxE effects (inferred).

3. Phenotypes

The core phenotype is a **laboratory abnormality** — absolute erythrocytosis — with downstream clinical signs and symptoms from hyperviscosity and the thrombotic tendency of a high hematocrit.

Phenotype	Type	Characteristics	Suggested HPO
Erythrocytosis / increased red cell mass	Lab abnormality	Congenital onset; lifelong; variable severity	HP:0001901 (Polycythemia)
Elevated hemoglobin/ hematocrit	Lab abnormality	Congenital; progressive if untreated	HP:0001899 (Increased hemoglobin)
Inappropriately normal/ high serum EPO	Lab abnormality	Characteristic; distinguishes from EPOR (ECYT1) low-EPO forms	HP:0003573 (Increased serum EPO)
Headache	Symptom	Hyperviscosity-related; variable	HP:0002315
Thrombosis / thromboembolism	Clinical sign	Risk rises with hematocrit; episodic	HP:0001907
Pulmonary hypertension	Clinical sign	Reported in severe germline cases	HP:0002092
Ischemic stroke	Clinical sign	Reported in severe germline cases	HP:0002140

In germline ECYT4, severe vascular complications (pulmonary hypertension, ischemic stroke) can occur, as in the pediatric case treated with belzutifan ([PMID: 40879399](#)). Tumor phenotypes (PPGL, somatostatinoma) and ocular/retinal vascular disease are predominantly features of the **mosaic** PZS form rather than typical germline erythrocytosis-only ECYT4, though the germline tumor-predisposing variant in [PMID: 23090011](#) shows overlap is possible. **Quality-of-life data** specific to ECYT4 (EQ-5D, SF-36) are not available in the reviewed literature.

4. Genetic / Molecular Information

- **Causal gene:** *EPAS1* / HIF2A (HGNC:3374; OMIM 603349; chromosome 2p21).
- **Pathogenic variants:** Missense substitutions in the ODDD clustering near P531 (D525G, L526F, G527K, A530S) and exon-9 variants (F374Y); A529V used in mouse modeling ([PMID: 36700397](#); [PMID: 23090011](#); [PMID: 31876943](#)).
- **Classification:** Pathogenic / likely pathogenic per ACMG, supported by functional luciferase/EPO-promoter assays (functional evidence, PS3) and recurrent clustering (PM1) ([PMID: 36700397](#)).

- **Variant type/class:** Missense point mutations.
- **Allele frequency:** Essentially absent from population databases (gnomAD) given rarity and pathogenicity (consistent with private/de novo and familial transmission; not explicitly quantified in sources).
- **Somatic vs germline:** Both occur — germline (heritable ECYT4) and postzygotic somatic mosaic (PZS). No loss of heterozygosity in associated tumors ([PMID: 23090011](#); [PMID: 37450881](#)).
- **Functional consequence:** Gain of function — increased HIF-2 α protein half-life and transcriptional activity ([PMID: 22931260](#)).
- **Modifier genes / epigenetics / chromosomal abnormalities:** None established for ECYT4.

5. Environmental Information

No environmental, lifestyle, or infectious agents cause ECYT4; it is a monogenic disorder. Physiologic modulators of the HIF-2 α /EPO axis (ambient oxygen tension/altitude, iron availability) may theoretically influence phenotype expression but are not established disease determinants ([PMID: 28263291](#); [PMID: 35618957](#)). Smoking and other causes of secondary erythrocytosis are relevant only as differential diagnoses to exclude.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. A germline gain-of-function missense variant in *EPAS1* alters the HIF-2 α ODDD near P531 → **leads to** impaired recognition of HIF-2 α by PHD2 (EGLN1). (*demonstrated — variant clustering + functional assays*, [PMID: 36700397](#))
2. Impaired PHD2-mediated prolyl hydroxylation → **results in** failure of pVHL E3-ligase recognition and loss of ubiquitin-proteasomal degradation of HIF-2 α . (*demonstrated*, [PMID: 39426935](#))
3. Escape from degradation → **leads to** stabilization and nuclear accumulation of HIF-2 α (increased protein half-life). (*demonstrated*, [PMID: 22931260](#); [PMID: 39426935](#))
4. Nuclear HIF-2 α dimerizes with HIF-1 β /ARNT and binds hypoxia-response elements → **results in** constitutive transactivation of *EPO*. (*demonstrated via EPO-promoter luciferase assays*, [PMID: 36700397](#); [PMID: 28263291](#))
5. Inappropriately elevated erythropoietin → **leads to** increased EPO-receptor signaling in erythroid progenitors and expanded erythropoiesis. (*demonstrated*, [PMID: 33840141](#))

6. Expanded red cell mass → **results in** erythrocytosis, elevated hematocrit, and increased blood viscosity → **leads to** headache, thrombosis, and (in severe cases) pulmonary hypertension and ischemic stroke. (*clinical*, [PMID: 40879399](#))

Branch (mosaic lesion): The identical gain-of-function lesion arising **post-zygotically** → produces mosaic tissue distribution → **leads to** Pacak–Zhuang syndrome: multiple PPGLs, duodenal somatostatinoma, pancreatic NETs, polycythemia, and developmental vascular/ocular anomalies ([PMID: 37450881](#); [PMID: 41518596](#); [PMID: 31876943](#)).

Upstream vs downstream: The mutation, hydroxylation escape, and HIF-2 α stabilization are upstream; EPO upregulation is the pivotal intermediate; erythrocytosis and its vascular sequelae are downstream.

Molecular pathway: HIF oxygen-sensing / hypoxia-response pathway (EGLN1/PHD2 → VHL → HIF-2 α → EPO). **Co-substrates:** molecular O₂, 2-oxoglutarate (α -ketoglutarate, CHEBI:30915), ferrous iron (CHEBI:29033) ([PMID: 28263291](#)).

Suggested GO terms: cellular response to hypoxia (GO:0071456); regulation of transcription from RNA Pol II promoter in response to hypoxia (GO:0061418); protein hydroxylation (GO:0018126); proteasome-mediated ubiquitin-dependent protein catabolic process (GO:0043161); positive regulation of erythrocyte differentiation (GO:0045648).

Suggested CL terms: EPO-producing renal interstitial fibroblast; erythroid progenitor cell (CL:0000038); erythroblast (CL:0000765); erythrocyte (CL:0000232).

7. Anatomical Structures Affected

- **Organ level (primary):** Kidney (renal interstitial EPO-producing cells; UBERON:0002113) as the EPO source; bone marrow (UBERON:0002371) as the site of expanded erythropoiesis.
Secondary/complication: blood/vasculature (UBERON:0000178), lungs (pulmonary hypertension; UBERON:0002048), brain (ischemic stroke; UBERON:0000955).
- **Body systems:** Hematopoietic and cardiovascular systems primarily. In the mosaic PZS branch, additionally the autonomic/adrenal system (adrenal medulla, UBERON:0001235; paraganglia), duodenum/pancreas (UBERON:0002114 / UBERON:0001264), and eye (retina/choroid, UBERON:0000966 / UBERON:0001776).
- **Tissue/cell level:** Erythroid lineage cells; renal peritubular fibroblasts; (mosaic) chromaffin cells, neuroendocrine cells, vascular endothelium.
- **Subcellular compartments:** Nucleus (GO:0005634) — site of HIF-2 α transcriptional action; cytoplasm — site of hydroxylation/degradation; proteasome (GO:0000502).

- **Lateralization:** Systemic/bilateral (hematologic); tumors in PZS are frequently multiple and bilateral/multifocal.

8. Temporal Development

- **Onset:** Congenital — erythrocytosis is present from early life, often detected in childhood or young adulthood; family history is typical (PMID: 41123216). In PZS, polycythemia precedes tumors, which arise in the 2nd–3rd decade (PMID: 39426935; PMID: 31091718).
- **Onset pattern:** Chronic/insidious.
- **Progression:** Erythrocytosis is stable-to-progressive and lifelong without treatment; tumor burden (PZS) can be progressive, recurrent, and metastatic (up to ~30%) (PMID: 39426935).
- **Remission/critical periods:** No spontaneous remission of erythrocytosis; it is treatment-controlled. Early detection permits intervention before thrombotic complications.

9. Inheritance and Population

- **Inheritance:** Autosomal dominant (germline ECT4) (PMID: 33840141; PMID: 23090011).
- **Penetrance/expressivity:** Appears high for erythrocytosis but with variable expressivity for vascular/tumor features; precise penetrance estimates are not established.
- **Epidemiology:** Very rare; ECT4 is one of the rarest familial erythrocytoses. Precise prevalence/incidence figures are not available. *EPAS1* variants account for ~3–6% of PPGLs (the mosaic phenotype context) (PMID: 39426935).
- **Sex ratio:** The *EPAS1*-related tumor phenotype is more frequent in females (PMID: 39426935); a sex skew for isolated germline erythrocytosis is not established.
- **Founder effects / consanguinity / anticipation / mosaicism:** No founder effect or consanguinity role (dominant). Postzygotic somatic mosaicism is the defining feature of the PZS branch. No genetic anticipation.

10. Diagnostics

- **Initial workup:** Confirm absolute erythrocytosis (elevated Hb/Hct, increased red cell mass); measure serum EPO (inappropriately normal/elevated in ECT4, contrasting with the subnormal EPO of EPOR-driven ECT1); exclude PV by *JAK2* V617F and exon 12 testing (PMID: 41123216).
- **Exclude secondary causes:** Hypoxia, high-oxygen-affinity hemoglobin variants, smoking, EPO-secreting tumors.

- **Genetic testing:** Targeted *EPAS1* sequencing or a hereditary-erythrocytosis gene panel (EPAS1, EGLN1, VHL, EPOR, HBB/HBA, BPGM, PIEZO1). For suspected mosaicism (PZS), deep sequencing of tumor/affected tissue rather than blood may be required, since variants can be absent or low-level in peripheral blood (PMID: 41123216; PMID: 37450881).
- **Differential diagnosis:** PV (JAK2+); other hereditary erythrocytoses (ECYT1/EPOR, ECYT2/VHL-Chuvash, ECYT3/EGLN1); secondary erythrocytosis.
- **Imaging:** Not required for isolated erythrocytosis; in PZS, functional/anatomic imaging for PPGL surveillance.

11. Outcome / Prognosis

With appropriate control of hematocrit, the hematologic prognosis of germline ECYT4 is generally good; the principal threat is **thrombosis/hyperviscosity**, with severe cases suffering pulmonary hypertension and ischemic stroke (PMID: 40879399). Disease-specific survival/mortality rates are not quantified in the reviewed literature. In the mosaic PZS branch, prognosis is driven by tumor behavior, including metastatic PPGL in up to ~30% (PMID: 39426935). **Prognostic factors:** hematocrit control, presence of vascular complications, and (in PZS) tumor multiplicity/metastasis.

12. Treatment

Modality	Intervention	Role / evidence	Suggested NCIT
Supportive	Therapeutic phlebotomy	First-line for symptom/hematocrit control (PMID: 41123216)	NCIT:C15843 (Therapeutic Phlebotomy)
Risk reduction	Low-dose aspirin + CV risk optimization	Advised to reduce thrombosis (PMID: 41123216)	NCIT:C287 (Aspirin)
Avoid	Cytoreductive therapy	Should be avoided (PMID: 41123216)	—
Targeted	Belzutifan (HIF-2 α inhibitor)	Normalized Hb without phlebotomy; mechanism-targeted; first reported in germline EPAS1 polycythemia (PMID: 40879399)	NCIT:C156989 (Belzutifan)
PZS tumors	Surgery $\pm$ systemic therapy	For PPGL/somatostatinoma; polycythemia only partially corrected by tumor removal (PMID: 31091718)	NCIT:C17173 (Surgical Procedure)

Pharmacogenomics / personalized medicine: Belzutifan exemplifies genotype-guided precision therapy — a drug directly targeting the mutated HIF-2 α protein. Its routine role in hereditary erythrocytosis is still being defined; guidelines note *"the role of HIF2A inhibitors remains unclear"* ([PMID: 41123216](#)), reflecting the gap between early case-level success and formal evidence.

13. Prevention

As a monogenic disorder, ECT4 cannot be prevented primarily. Relevant measures are: - **Secondary prevention:** Early detection via family screening and genetic testing; cascade testing of at-risk relatives given autosomal dominant inheritance. - **Tertiary prevention:** Hematocrit control (phlebotomy/belzutifan), aspirin, and CV risk-factor management to prevent thrombosis; in PZS, PPGL surveillance ([PMID: 41123216](#); [PMID: 40879399](#)). - **Counseling:** Genetic counseling for affected families; prenatal/preimplantation options are theoretically available for known family variants. No immunization is applicable.

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** Human *EPAS1* (NCBI Gene 2034) has a mouse ortholog *Epas1* (NCBI Gene 13819). The oxygen-sensing pathway (EGLN1/VHL/HIF-2 α /EPO) is deeply conserved across mammals.
- **Natural disease in other species:** No well-characterized naturally occurring *EPAS1* gain-of-function erythrocytosis is documented in companion animals or wildlife in the reviewed sources. (*EPAS1* is notable in high-altitude adaptation genetics, e.g., Tibetan human populations and some animals, but that is adaptive variation, not disease.)
- **Zoonotic potential:** Not applicable (non-infectious).

15. Model Organisms

- **Mouse (primary model):** Transgenic mice expressing gain-of-function *Epas1*/HIF-2 α (including *Epas1*^{A529V}) recapitulate polycythemia, vascular malformations, neural tube defects, and ocular/retinal/choroidal vascular changes (PMID: 31091718; PMID: 31876943; PMID: 37450881).
 - **Model type:** Mammalian, transgenic/knock-in gain-of-function.
 - **Phenotype recapitulation:** Strong for polycythemia and the developmental/vascular/ocular PZS features; the model has clarified natural history and the pathophysiologic role of HIF-2 α .
 - **Limitations:** Mouse models of mosaic PZS may not fully reproduce the human tumor spectrum or variant-specific severity; germline erythrocytosis-only phenotypes versus mosaic tumor phenotypes depend on expression timing and tissue distribution.
 - **Resources:** MGI for *Epas1* alleles; NIH PPGL translational program models.
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Mechanistic Model / Interpretation

Germline EPAS1 gain-of-function variant (e.g., D525G/L526F/G527K/A530S near P531; F374Y exon 9)

↓
Impaired PHD2 (EGLN1) prolyl-hydroxylation of HIF-2α at P531

↓
Loss of pVHL recognition → no ubiquitin-proteasomal degradation

↓
HIF-2α stabilized (↑ half-life) → nuclear accumulation

↓
HIF-2α:HIF-1β binds HRE → constitutive EPO transactivation

↓
↑ Serum EPO (inappropriately normal/high) → ↑ erythropoiesis

↓
Erythrocytosis / ↑ hematocrit / hyperviscosity

↓
Headache, thrombosis

↓
Pulmonary hypertension, ischemic stroke
(severe cases)

— Branch: identical lesion arising POST-ZYGOTICALLY (mosaic) →
Pacak-Zhuang syndrome: multiple PPGL + somatostatinoma +
pancreatic NET + polycythemia + ocular/vascular + Chiari I

Comparative nosology of Mendelian familial erythrocytoses:

Subtype	Gene	Mechanism	Inheritance	Serum EPO
ECYT1	<i>EPOR</i>	Gain-of-function (primary)	AD	Low/subnormal
ECYT2 (Chuvash)	<i>VHL</i>	Loss-of-function (O ₂ -sensing)	AR	Elevated
ECYT3	<i>EGLN1</i> / <i>PHD2</i>	Loss-of-function (O ₂ -sensing)	AD	Normal/elevated
ECYT4	<i>EPAS1</i> / <i>HIF2A</i>	Gain-of-function (O ₂ -sensing)	AD	Normal/ elevated

All secondary (O_2 -sensing) subtypes converge on constitutive EPO signaling (PMID: 33840141). The key conceptual insight is that ECYT4 is the **gain-of-function endpoint** of the same pathway whose loss-of-function endpoints (VHL, EGLN1) produce ECYT2/ECYT3 — all four classic subtypes are reducible to "too much EPO signal," reached by different molecular routes.

Evidence Base

PMID	Title (abbrev.)	Contribution
36700397	<i>Comprehensive EPAS1 cohort</i>	Defines causal germline variants clustering near P531; functional validation (F001)
33840141	<i>Congenital erythrocytosis</i>	Places EPAS1 GoF in O ₂ -sensing nosology; constitutive EPO (F002, F009)
39426935	<i>HIF-2α in PPGL pathogenesis</i>	Molecular stabilization mechanism; tumor demographics (F002, F003)
37450881	<i>Pacak–Zhuang syndrome</i>	Defines mosaic syndrome; mouse model insights (F003, F007)
40879399	<i>Belzutifan in EPAS1 erythrocytosis</i>	First mechanism-targeted therapy success (F004, F006)
22931260	<i>Somatic HIF2A GoF, 2012</i>	Landmark discovery; ↑ half-life/activity (F005)
23090011	<i>Germline EPAS1 F374Y</i>	Proves heritable germline GoF; no tumor LOH (F005)
41123216	<i>JAK2-unmutated erythrocytosis 2026</i>	Diagnostic/management framework (F006)
28263291	<i>Iron suppresses EPO via HIF-2α</i>	HIF-2α as EPO regulator; iron tuning (F008)
35618957	<i>Iron–erythropoiesis crosstalk</i>	IRP/IRE control of HIF-2α (F008)
31876943	<i>Retinal/choroidal changes in PZS</i>	Ocular phenotype; <i>Epas1</i> ^{A529V} mouse (F003, F007)
31091718	<i>Transgenic PZS mouse</i>	Model of mosaic GoF; polycythemia before tumors (F007)
31185588	<i>Chiari I in EPAS1 syndrome</i>	Expands developmental phenotype (F003)
41518596	<i>Pancreatic NETs in PZS</i>	Expands tumor spectrum (F003)
27659016	<i>HIF2A PPGL expression cluster</i>	HIF2A tumors form discrete pseudohypoxic subcluster

Consistency: The 15 papers are mutually reinforcing, with no direct contradictions. The main tension is interpretive: case-level success with belzutifan ([PMID: 40879399](#)) versus the 2026 guideline's cautious "role remains unclear" ([PMID: 41123216](#)) — reflecting an evidence-maturity gap rather than disagreement.

Supported and Refuted Hypotheses

No hypotheses were formally refuted during the investigation. The following working hypotheses were **supported** by the evidence:

- **H1 (supported):** ECYT4 is caused by germline gain-of-function *EPAS1* variants near P531 → confirmed (F001, [PMID: 36700397](#)).
 - **H2 (supported):** The mechanism is escape from PHD2/VHL degradation → HIF-2α stabilization → EPO upregulation → confirmed (F002, F003, F008).
 - **H3 (supported):** Germline and mosaic forms are two expressions of the same lesion → confirmed (F005, F003).
 - **H4 (supported):** HIF-2α inhibition (belzutifan) is a rational, effective therapy → supported by first case report (F004/F006), with the caveat that formal evidence is still limited.
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Limitations and Knowledge Gaps

1. **Epidemiology:** No reliable prevalence/incidence figures for germline ECYT4; it is simply described as very rare. Penetrance and expressivity estimates are not quantified.
2. **Germline vs mosaic phenotype boundary:** Much of the deep phenotyping (tumors, ocular, Chiari) derives from the **mosaic** PZS form; the degree to which isolated germline ECYT4 patients develop tumors is less well characterized, though overlap exists ([PMID: 23090011](#)).
3. **Therapy evidence:** Belzutifan data in germline erythrocytosis are limited to case-level reports; no randomized/controlled data, long-term safety, or dosing standards exist for this indication.
4. **Quality-of-life / natural history:** No ECYT4-specific QoL instruments or longitudinal cohort outcome data were identified.

5. **Allele frequencies and ACMG population criteria:** Precise gnomAD frequencies for individual ECYT4 variants were not extracted.
6. **No primary data analysis:** This report is a literature synthesis; no patient-level datasets were available for independent statistical testing.

Proposed Follow-up Experiments / Actions

1. **Belzutifan evidence development:** Design a prospective registry or basket trial of HIF-2 α inhibition in genetically confirmed germline *EPAS1* erythrocytosis, with hematocrit, EPO, thrombotic events, pulmonary pressures, and safety (hypoxia, anemia) as endpoints.
2. **Genotype–phenotype mapping:** Correlate specific ODDD variants (P531-proximal vs exon-9) with erythrocytosis severity and tumor risk to refine surveillance recommendations and penetrance estimates.
3. **Tumor-risk stratification in germline carriers:** Systematically screen germline ECYT4 families for PPGL/somatostatinoma to quantify the germline tumor penetrance currently inferred mainly from mosaic cases.
4. **Population screening:** Query gnomAD/large biobanks for *EPAS1* ODDD variants to estimate true allele frequencies and carrier burden.
5. **Mechanistic refinement:** Use the *Epas1*^{A529V} (and new knock-in) mouse models plus structural/AlphaFold analysis of the HIF-2 α ODDD to quantify how each variant perturbs PHD2 docking, informing variant classification (PS3).
6. **Iron-axis modulation:** Formally test whether iron status (deliberately lowered by phlebotomy) interacts with HIF-2 α stability to modulate ECYT4 severity ([PMID: 28263291](#)).

Report compiled from 9 confirmed findings and 15 primary-literature sources across a 5-iteration autonomous investigation. Evidence source types: predominantly human clinical (cohorts/case reports) and model organism (transgenic mouse), supported by in vitro functional assays.