

Familial Erythrocytosis 5 (ECYT5): Comprehensive Disease Characteristics Report

Disease: Familial Erythrocytosis 5 (ECYT5) **MONDO ID:** MONDO:0033483 · **OMIM:** #617907 · **Causal gene:** *EPO* (HGNC:3415), chromosome 7q22.1 **Category:** Mendelian (autosomal dominant) **Evidence base:** Individual-family case reports + functional studies; disease-level resources (OMIM/Orphanet) and broader erythrocytosis reviews.

Summary

Familial Erythrocytosis 5 (ECYT5) is an ultra-rare, autosomal dominant form of secondary (EPO-driven) erythrocytosis caused by germline gain-of-function variants in the erythropoietin structural gene (*EPO*) itself. It is biologically distinctive among the hereditary erythrocytoses because, whereas the other familial forms disrupt the *EPO receptor* (ECYT1/*EPOR*), the oxygen-sensing pathway (ECYT2/*VHL*, ECYT3/*EGLN1*, ECYT4/*EPAS1*), or hemoglobin oxygen affinity, ECYT5 is the only one in which the gene encoding erythropoietin is the site of the lesion. The result is constitutive or ectopic overproduction of erythropoietin uncoupled from the normal hypoxia-sensing feedback loop, driving excessive red-cell production through an otherwise-normal signaling cascade.

Two mechanistically distinct causal variants are documented. The founding kindred ([PMID: 29514032](#)) carried a single-nucleotide frameshift deletion (*EPO* c.32delG) that paradoxically silences translation of the main *EPO* mRNA while rerouting ribosomes to a normally non-coding transcript initiated from an alternative promoter in intron 1 — thereby producing excess erythropoietin from a frameshifted allele. A second kindred ([PMID: 41574959](#)) carried a promoter variant (*EPO* c.-136 G>A) that creates a new hypoxia-response element (HRE) on the reverse strand, driving increased, oxygen-independent *EPO* transcription confirmed in CRISPR-edited Hep3B cells and luciferase reporter assays. Both lesions sit upstream of the erythropoietin receptor (*EPOR*)–JAK2–STAT5 axis and over-drive a normal pathway rather than altering the receptor or its downstream effectors.

Clinically, ECT5 manifests as lifelong, isolated erythrocytosis (elevated hemoglobin and hematocrit) with inappropriately normal-to-elevated serum EPO and a positive family history, but without the leukocytosis, thrombocytosis, or splenomegaly of polycythemia vera (PV). The principal risks arise from hyperviscosity and thrombosis. Management is extrapolated from PV and the broader category of JAK2-unmutated erythrocytosis: hematocrit-lowering phlebotomy for symptom control, low-dose aspirin, and cardiovascular risk optimization, while **cytoreductive therapy is explicitly avoided** because the disorder is non-clonal. Disease biology and the consequences of sustained high hematocrit are illuminated by EPO-overexpressing transgenic *tg6* mice and by CRISPR-edited human hepatoma cell models.

Key Findings

Finding 1 — ECT5 is an autosomal dominant erythrocytosis caused by a gain-of-function *EPO* mutation

The founding description (Zmajkovic et al., *A Gain-of-Function Mutation in EPO in Familial Erythrocytosis*, *NEJM* 2018) identified an *EPO* mutation that cosegregated with autosomal dominant erythrocytosis in a single large family with a logarithm-of-the-odds (LOD) score of 3.3 — statistically significant genetic linkage. The verified quote establishes the core genetics: *"We identified a mutation in EPO that cosegregated with disease with a logarithm of the odds (LOD) score of 3.3 in a family with autosomal dominant erythrocytosis. This mutation, a single-nucleotide deletion (c.32delG), introduces a frameshift in exon 2"* (PMID: 29514032). This defines the gene (*EPO*, HGNC:3415, chromosome 7q22.1), the inheritance pattern (autosomal dominant), and the identifiers (OMIM #617907; MONDO:0033483).

Finding 2 — A paradoxical gain-of-function: the frameshift silences the main transcript but activates a normally non-coding intron-1 transcript

The most counterintuitive feature of c.32delG is that a frameshift — usually a loss-of-function lesion — produces a *gain* of EPO. Per Zmajkovic et al., the deletion *"introduces a frameshift in exon 2 that interrupts translation of the main EPO messenger RNA (mRNA) transcript but initiates excess production of erythropoietin from what is normally a noncoding EPO mRNA transcribed from an alternative promoter located in intron 1"* (PMID: 29514032). The frameshift

unmasks an alternative, intron-1-driven transcript whose translation yields functional erythropoietin in excess — explaining how a single-base coding deletion produces a secondary (high-EPO) rather than primary erythrocytosis.

Finding 3 — A second, promoter-based mechanism: *EPO* c.-136 G>A creates a new hypoxia-response element

A five-generation kindred with autosomal dominant erythrocytosis carried a germline *EPO* promoter variant, c.-136 G>A (Lanikova et al., 2026). The variant creates a new HRE consensus sequence on the reverse strand, and this gain of function was confirmed functionally: *"This mutation creates a new hypoxia response element (HRE) consensus sequence on the reverse strand suggesting a gain of function mutation. CRISPR/Cas9-edited Hep3B cells harboring the c.-136 G>A variant had increased EPO mRNA and protein expression under both normoxic and hypoxic conditions compared to wild-type cells"* (PMID: 41574959). Luciferase assays confirmed increased mutant-promoter transcription, and urine/plasma isoelectric focusing showed a more basic EPO isoform pattern consistent with decreased renal and increased non-renal (ectopic) EPO production. This establishes a *second, independent* route to ECT5 — a cis-regulatory promoter variant — broadening the mutational spectrum.

Finding 4 — EPO-overexpressing *tg6* transgenic mice model the disease and reveal multi-organ/vascular consequences

The *tg6* mouse constitutively overexpresses human EPO in a hypoxia-independent manner — directly paralleling the oxygen-uncoupled EPO excess of ECT5 — reaching hematocrit up to 0.89: *"transgenic mouse line (tg6) that constitutively overexpresses erythropoietin (Epo) in a hypoxia-independent manner; thereby reaching hematocrit levels of up to 0.89"* (PMID: 16690772). Chronic excessive erythrocytosis caused hepatic, renal, neuronal, and muscular degeneration and reduced lifespan (PMID: 16690772); endothelial activation and damage with reduced brain-vessel density (PMID: 16254128); near-abolition of the endothelial glycocalyx (wild-type 0.52 μm vs *tg6* 0.13 μm ; $P < 0.001$) (PMID: 21859826); and pregnancy loss from impaired uterine arteriogenesis rescued by lowering hematocrit: *"pregnant human erythropoietin-overexpressing (plasma levels elevated 12-fold) mice (termed tg6 mice) suffering from excessive erythrocytosis generally abort at midgestation unless their hematocrit of 0.85 is drastically lowered"* (PMID: 18256329). These data causally link the degree of erythrocytosis (hematocrit) — not EPO per se — to vascular/end-organ harm, supporting hematocrit-lowering as the central therapeutic lever.

Finding 5 — Diagnostic framework and management for EPO-driven erythrocytosis

The diagnostic approach begins by excluding PV: *"Foremost in the evaluation of erythrocytosis is the exclusion of PV through JAK2 (inclusive of exons 12-15) mutation screening"* (Gangat/Szuber/Tefferi, 2023; PMID: 36966432). Thereafter, serum EPO and germline mutation screening are used: subnormal EPO points to EPOR (ECYT1), whereas oxygen-sensing/EPO defects such as ECYT5 show normal/elevated EPO with a normal P50. High-oxygen-affinity hemoglobins (left-shifted P50) are a key differential (PMID: 21511372; PMID: 33456185). Management targets are borrowed from PV data — maintain hematocrit <45% via phlebotomy: *"received only phlebotomy (PHL) or HU to maintain the hematocrit level < 45%"* (PMID: 28699191).

Finding 6 — Clinical phenotype: isolated erythrocytosis with hyperviscosity symptoms and thrombotic risk

ECYT5 presents as lifelong, isolated erythrocytosis with inappropriately normal or elevated serum EPO and a positive family history, without the leukocytosis, thrombocytosis, or splenomegaly of PV: *"Hereditary erythrocytosis (HE) is lifelong and typically associated with a positive family history. Subnormal serum erythropoietin (EPO) suggests an EPO receptor mutation"* (PMID: 41347984) — with ECYT5 falling into the normal/high EPO category. Hyperviscosity manifestations shared by erythrocytosis states include headache, visual disturbances, pruritus, and erythromelalgia; splenomegaly is PV-specific: *"Polycythemia vera is characterized by headache, visual disturbances, pruritus, erythromelalgia and splenomegaly"* (PMID: 42557631). In the original kindred, c.32delG cosegregated with the phenotype (LOD 3.3; PMID: 29514032).

Finding 7 — Epidemiology and a management caveat: ultra-rare, and cytoreduction should be avoided

JAK2-unmutated erythrocytosis has a reported incidence of 0.13%–4.1% (*"Incidence has been reported to be between 0.13% and 4.1%"*; PMID: 41347984), but ECYT5 specifically is vanishingly rare — a handful of families worldwide (PMID: 29514032; PMID: 41574959). The 2026 management update is explicit for non-clonal (hereditary/idiopathic) erythrocytosis: *"Cytoreductive therapy should be avoided. Phlebotomy should be considered for symptom control. Cardiovascular risk optimization and low-dose aspirin are advised"* (PMID: 41123216).

Finding 8 — The EPO signaling causal chain

Physiologically, HIF-2 regulates EPO synthesis in response to hypoxia: "*HIF-2 has emerged as the transcription factor that regulates EPO synthesis in the kidney and liver*" (Haase, 2013; [PMID: 23291219](#)). EPO then binds EPOR on erythroid progenitors, activating JAK2 and downstream STAT5, PI3K/AKT, and MAPK, which inhibit apoptosis and promote erythroid proliferation/differentiation: "*EPO activates the JAK2-STAT5 pathway, and two tyrosine residues (Y343, Y401) in the cytoplasmic domain of EPOR are important for STAT5 activation*" ([PMID: 9664155](#)). In ECYT5 the lesion is *upstream* of this axis: a gain-of-function *EPO* variant causes constitutive/ectopic EPO overproduction uncoupled from hypoxia, over-driving the otherwise-normal cascade.

Report by Research Section

1. Disease Information

ECYT5 is a hereditary, EPO-driven (secondary-type) erythrocytosis: a lifelong increase in red-cell mass (elevated hemoglobin/hematocrit) caused by germline gain-of-function variants in the erythropoietin gene (*EPO*) itself. It is the fifth-defined familial erythrocytosis locus and the only one in which the *EPO* structural gene is mutated, as opposed to its upstream oxygen-sensing regulators (*VHL*/ECYT2, *EGLN1*/ECYT3, *EPAS1*/ECYT4) or its receptor (*EPOR*/ECYT1) ([PMID: 29514032](#)).

Key identifiers: MONDO:0033483; OMIM #617907 (ERYTHROCYTOSIS, FAMILIAL, 5); gene *EPO*, HGNC:3415, NCBI Gene 2056, chromosome 7q22.1; Orphanet within "Familial erythrocytosis" group (no separate well-populated ECYT5 code); ICD-10 D75.1 (Secondary polycythaemia) / ICD-11 3A51; MeSH closest "Polycythemia" (D011087).

Synonyms: ECYT5; Familial erythrocytosis type 5; EPO-related familial erythrocytosis; autosomal dominant erythrocytosis due to *EPO* mutation.

Information source: Aggregated disease-level resources (OMIM, Orphanet) plus individual-family reports (two kindreds) and in-vitro functional assays. Not EHR-derived.

2. Etiology

Primary cause — genetic. ECT5 is monogenic: a heterozygous gain-of-function germline *EPO* variant causes inappropriate EPO overproduction uncoupled from oxygen-sensing feedback. Two causal variants are documented: (1) **c.32delG** (exon-2 frameshift), cosegregating with disease at LOD 3.3 ([PMID: 29514032](#)); (2) **c.-136 G>A** (promoter variant creating a novel HRE) ([PMID: 41574959](#)).

- **Genetic risk factors:** The causal *EPO* allele itself; a single mutant allele confers the phenotype (dominant). No susceptibility loci or modifier genes established.
- **Environmental risk factors:** None causal. Exogenous drivers of red-cell mass (altitude/chronic hypoxia, smoking/CO, androgens, SGLT2 inhibitors, ESAs) could additively worsen hematocrit (inferred; [PMID: 42557631](#), [PMID: 41123216](#)).
- **Protective factors:** None specific; lowering hematocrit (phlebotomy) and avoiding additive erythropoietic exposures are mitigating.
- **Gene–environment interactions:** Plausible additive effect of hypoxia/erythropoietic drugs on the genetically elevated baseline (inferred, not formally studied in ECT5).

3. Phenotypes

ECT5 is fundamentally a laboratory-defined phenotype; clinical symptoms, when present, arise from hyperviscosity and attendant thrombotic risk.

Phenotype	Type	HPO term	Onset / course	Frequency
Erythrocytosis/ polycythemia (↑ RBC mass)	Lab abnormality	HP:0001901 (Polycythemia)	Lifelong, early, stable	Obligate (defining)
Elevated hemoglobin/ hematocrit	Lab abnormality	HP:0001899 (Increased hematocrit) / HP:0001900	Lifelong	Obligate
Increased serum EPO (inappropriately normal/high)	Lab abnormality	HP:0020059 (Increased circulating EPO)	Lifelong	Characteristic
Headache	Symptom	HP:0002315	Episodic, with high Hct	Variable
Pruritus	Symptom	HP:0000989	Variable	Occasional
Erythromelalgia	Clinical sign	HP:0200071	Episodic	Occasional
Plethora / facial redness	Physical sign	HP:0001050 (Plethora)	Chronic	Variable
Visual disturbance / dizziness	Symptom	HP:0000504 / HP:0002321	Episodic	Variable
Thrombosis (arterial/venous)	Clinical complication	HP:0001907 (Thromboembolism)	Event-driven, adult	Risk; undefined for ECYT5

Symptom source: hyperviscosity complex shared across erythrocytosis ([PMID: 42557631](#)); unlike PV, ECYT5 shows no splenomegaly, leukocytosis, or thrombocytosis ([PMID: 41347984](#)). **Severity/progression:** generally mild–moderate, chronic, non-progressive; variable between individuals. **Quality-of-life impact:** not formally measured (no EQ-5D/SF-36 data for ECYT5); driven mainly by thrombotic events and recurrent phlebotomy.

4. Genetic / Molecular Information

Causal gene: *EPO* (HGNC:3415; OMIM *133170; chr 7q22.1; UniProt P01588).

Pathogenic variants (germline, heterozygous, AD): - **c.32delG** — exon-2 frameshift; paradoxical gain of function in EPO output via an intron-1 alternative transcript ([PMID: 29514032](#)). - **c.-136 G>A** — promoter/regulatory variant; gain of function via novel HRE ([PMID: 41574959](#)). - Note: the pathogenic lesions lie in exon-2 frameshift context, the promoter, and intron 1 — **standard exon-focused panels can miss them.**

Variant classification (ACMG/AMP): Pathogenic/likely pathogenic based on cosegregation (LOD 3.3), functional confirmation (CRISPR-edited Hep3B, luciferase, isoelectric focusing), and absence in population controls. **Allele frequency:** essentially absent from gnomAD (private family variants). **Origin:** germline. **Functional consequence:** gain of function (increased EPO production) — a translational/transcriptional rerouting that augments EPO output rather than an activating protein change.

Modifier genes: none established. **Epigenetic information:** no disease-specific methylation/histone data; c.-136 G>A acts via a cis-regulatory (HRE) element, not epigenetic modification. **Chromosomal abnormalities:** none — ECT5 is a point/indel disorder.

5. Environmental Information

- **Environmental factors:** None causal; hypoxic exposures (altitude, cardiopulmonary disease, CO) can compound the erythrocytosis (inferred).
- **Lifestyle factors:** Smoking, androgen/anabolic-steroid use, testosterone therapy, SGLT2 inhibitors, and ESAs independently raise hematocrit and would aggravate ECT5 ([PMID: 41123216](#), [PMID: 42557631](#)).
- **Infectious agents:** Not applicable.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. A germline **gain-of-function EPO variant** (c.32delG frameshift **or** c.-136 G>A promoter HRE) is present in EPO-producing cells. (*demonstrated: linkage + functional assays*)
2. **Frameshift branch (c.32delG):** translation of the main EPO mRNA is interrupted, **but** excess erythropoietin is produced from a normally non-coding alternative EPO transcript driven by an intron-1 promoter → **leads to** EPO overproduction (*demonstrated*). **Promoter branch (c.-136 G>A):** a new reverse-strand HRE **results in** increased EPO transcription under normoxia and hypoxia, with a shift toward non-renal/ectopic EPO → **leads to** EPO overproduction (*demonstrated in Hep3B + luciferase*).

3. Both branches **result in** constitutive/ectopic EPO overproduction **uncoupled from oxygen sensing** (inappropriately normal-to-high serum EPO despite normal oxygenation). *(demonstrated clinically)*
4. Circulating EPO **binds** EPOR on erythroid progenitors, **activating** JAK2 → STAT5 (and PI3K/AKT, MAPK). *(inferred from canonical EPO biology; PMID: 9664155)*
5. This **inhibits** erythroid-progenitor apoptosis and **promotes** proliferation/differentiation. *(demonstrated in EPO biology)*
6. Expanded red-cell mass **raises** hematocrit → increases whole-blood viscosity. *(demonstrated)*
7. Hyperviscosity **leads to** impaired microcirculation, endothelial activation, and increased thrombotic risk plus hyperviscosity symptoms; at extreme Hct it **causes** endothelial/glycocalyx damage and multi-organ degeneration (tg6 mice; PMID: 16690772, PMID: 16254128, PMID: 21859826). *(model-organism evidence + clinical inference)*

Detail by category. *Molecular pathways:* EPO–EPOR–JAK2–STAT5 (primary), PI3K/AKT and RAS–MAPK (secondary) (PMID: 9664155); the upstream physiologic regulator normally dysregulated is HIF-2/EPAS1, controlling renal/hepatic EPO synthesis (PMID: 23291219). *Cellular processes:* anti-apoptosis and proliferation of erythroid progenitors; erythron expansion. *Protein dysfunction:* not altered EPO structure — the defect is excess production of functional EPO (gain of function in dosage/expression); isoelectric focusing shows a more basic, non-renal-type EPO isoform in the promoter-variant family (PMID: 41574959). *Metabolic/biochemical:* secondary to erythrocytosis (↑ iron utilization, possible phlebotomy-induced iron deficiency; altered 2,3-BPG/oxygen delivery in models, PMID: 17365666). *Immune:* none primary; chronic hyperviscosity-associated endothelial inflammation is a downstream model finding. *Tissue-damage:* hyperviscosity, endothelial activation, reduced glycocalyx, impaired arteriogenesis (model organism; PMID: 18256329, PMID: 21859826). **Ontology suggestions:** GO:0038162 (erythropoietin-mediated signaling pathway), GO:0030218 (erythrocyte differentiation), GO:0043066 (negative regulation of apoptotic process); CL:0000038 (erythroid progenitor cell), CL:0000765 (erythroblast), CL:0000115 (endothelial cell, downstream); UBERON:0002113 (kidney), UBERON:0002107 (liver), UBERON:0002371 (bone marrow).

7. Anatomical Structures Affected

- **Organ level — primary:** Bone marrow (UBERON:0002371, erythroid expansion); EPO-producing kidney (UBERON:0002113) and liver (UBERON:0002107) as the site of the lesion's expression; blood/vasculature (UBERON:0000178) as effector compartment.

- **Secondary/complication organs:** Cerebral and coronary vasculature, splanchnic/portal veins (thrombosis sites); in models, liver, kidney, brain, peripheral nerve, and skeletal muscle degenerate under extreme Hct (PMID: 16690772).
- **Body systems:** Hematologic, cardiovascular (thrombosis/hyperviscosity); nervous (headache; neuropathy in models).
- **Tissue/cell level:** Erythroid lineage (CL:0000764), erythroid progenitors (CL:0000038); vascular endothelial cells (CL:0000115) as downstream targets.
- **Subcellular (GO CC):** EPO secreted (GO:0005615 extracellular space); signaling at plasma membrane/receptor complex (GO:0005886).
- **Localization/laterality:** Systemic/bilateral (blood-borne); thrombotic events are focal and variable.

8. Temporal Development

- **Onset:** Congenital/early-life predisposition; lifelong erythrocytosis typically detected in childhood–adulthood (PMID: 41347984); chronic/insidious pattern.
- **Progression:** Stable, non-progressive erythrocytosis with no transformation to malignancy — a key contrast with PV (non-clonal).
- **Course:** Lifelong/chronic; "remission" only via treatment-induced hematocrit lowering (phlebotomy); no spontaneous remission; no anticipation (point/indel mutation).
- **Critical periods:** Pregnancy (hyperviscosity risk; model shows hematocrit-dependent pregnancy loss, PMID: 18256329) and perioperative/immobilization windows for thrombosis.

9. Inheritance and Population

- **Inheritance:** Autosomal dominant (single heterozygous *EPO* gain-of-function allele; cosegregation LOD 3.3; PMID: 29514032).
- **Penetrance/expressivity:** High penetrance for the erythrocytosis trait within kindreds; variable clinical expressivity (symptomatic burden differs).
- **Anticipation / germline mosaicism / consanguinity:** Not expected/not relevant (dominant). **Founder effects:** none — private family variants.
- **Carrier frequency:** Not applicable (dominant); variants essentially absent from gnomAD.
- **Epidemiology:** Ultra-rare — a handful of families worldwide; within JAK2-unmutated erythrocytosis (incidence 0.13%–4.1%, PMID: 41347984), but a vanishingly small subset. No ECYT5-specific prevalence/incidence figures exist.

- **Demographics:** Both sexes affected (autosomal; thresholds sex-specific); no ethnic predilection; variants are family-private.

10. Diagnostics

Diagnostic algorithm (PMID: 41347984, PMID: 41123216, PMID: 36966432): 1. Confirm true erythrocytosis ($\uparrow$ Hgb/Hct vs age/sex thresholds; exclude relative/apparent polycythemia). LOINC: hemoglobin 718-7; hematocrit 4544-3; erythropoietin 14743-9. 2. **Exclude PV** — screen *JAK2* (exons 12–15); ECYT5 is *JAK2*-wild-type with normal WBC/platelets and no splenomegaly. 3. **Serum EPO:** inappropriately normal or elevated in ECYT5 (contrast: subnormal $\rightarrow$ EPOR mutation/PV). 4. **P50:** normal in ECYT5 (contrast: low/left-shifted $\rightarrow$ high-oxygen-affinity hemoglobin; PMID: 21511372, PMID: 33456185). 5. **Genetic testing:** sequence *EPO* including exon 2, the promoter (5'), and intron 1 — exon-only panels can miss ECYT5 variants. Hereditary-erythrocytosis gene panels (*EPOR*, *VHL*, *EGLN1*, *EPAS1*, *EPO*, *HBA/HBB*, *BPGM*, *PIEZO1*) via NGS; WES/WGS when panel-negative (noting promoter variants may be missed by exome-only approaches).

Clinical tests/biomarkers: CBC, serum EPO, P50, *JAK2*; the genetic variant is the definitive biomarker. Isoelectric focusing of urine/plasma EPO can reveal a non-renal isoform pattern (PMID: 41574959). Bone marrow biopsy not required (no clonal myeloproliferation).

Differential diagnosis: PV (*JAK2*+); EPOR-mutant PFCP (low EPO); oxygen-sensing erythrocytoses (*VHL*/Chuvash, *EGLN1*, *EPAS1*); high-oxygen-affinity hemoglobinopathies (low P50); acquired secondary causes. **Screening:** cascade genetic testing of at-risk first-degree relatives in known kindreds.

11. Outcome / Prognosis

- **Survival/life expectancy:** Generally favorable; ECYT5 does not transform to leukemia/myelofibrosis (unlike PV). No ECYT5-specific survival statistics.
- **Mortality/morbidity:** Driven by thrombosis (arterial/venous) from hyperviscosity; event rates undefined for ECYT5. Models under extreme Hct show reduced lifespan and multi-organ damage (PMID: 16690772).
- **Complications:** Thromboembolism (stroke, MI, venous/splanchnic thrombosis), hyperviscosity symptoms, pregnancy complications (inferred/model).
- **Prognostic factors:** Degree of hematocrit elevation, prior thrombosis, conventional cardiovascular risk factors (extrapolated from PV cohorts where CV risk factors and prior thrombosis predict events).

- **Recovery:** Hematocrit control is effective at reducing hyperviscosity; the genetic driver is lifelong.

12. Treatment

No ECYT5-specific trials exist; management is extrapolated from hereditary/secondary erythrocytosis and PV data.

- **Therapeutic phlebotomy / venesection** — mainstay to lower hematocrit and control symptoms (NCIT: Therapeutic Phlebotomy). Target historically <45% (from PV; [PMID: 28699191](#)), individualized for secondary erythrocytosis ([PMID: 41123216](#)).
- **Low-dose aspirin** — antiplatelet thromboprophylaxis: *"Cardiovascular risk optimization and low-dose aspirin are advised"* ([PMID: 41123216](#)) (NCIT: Aspirin, C287).
- **Cardiovascular risk-factor optimization** — blood pressure, smoking cessation, avoid additive erythropoietic agents (androgens, SGLT2i, ESAs).
- **Cytoreduction (hydroxyurea)** — **generally AVOIDED** in non-clonal hereditary erythrocytosis: *"Cytoreductive therapy should be avoided"* ([PMID: 41123216](#)) (NCIT: Hydroxyurea, C546).
- **Experimental/targeted:** Role of HIF-2 α inhibitors remains unclear for hereditary erythrocytosis ([PMID: 41123216](#)); no gene/cell/RNA therapy exists. **Pharmacogenomics:** none established.
- **Supportive:** Hydration, standard anticoagulation for thrombotic events, iron monitoring given repeated phlebotomy.

13. Prevention

- **Primary prevention:** Not possible (germline). Focus on genetic counseling and avoidance of additive erythrocytosis triggers.
- **Secondary prevention:** Cascade genetic screening of first-degree relatives; early hematocrit monitoring; prompt phlebotomy.
- **Tertiary prevention:** Thromboprophylaxis (aspirin), hematocrit control, cardiovascular risk management.
- **Genetic counseling:** Autosomal dominant $\rightarrow$ 50% transmission risk; prenatal/preimplantation testing technically feasible for a known family variant but rarely pursued given the generally manageable course.
- **Immunization / public-health / environmental:** Not applicable.

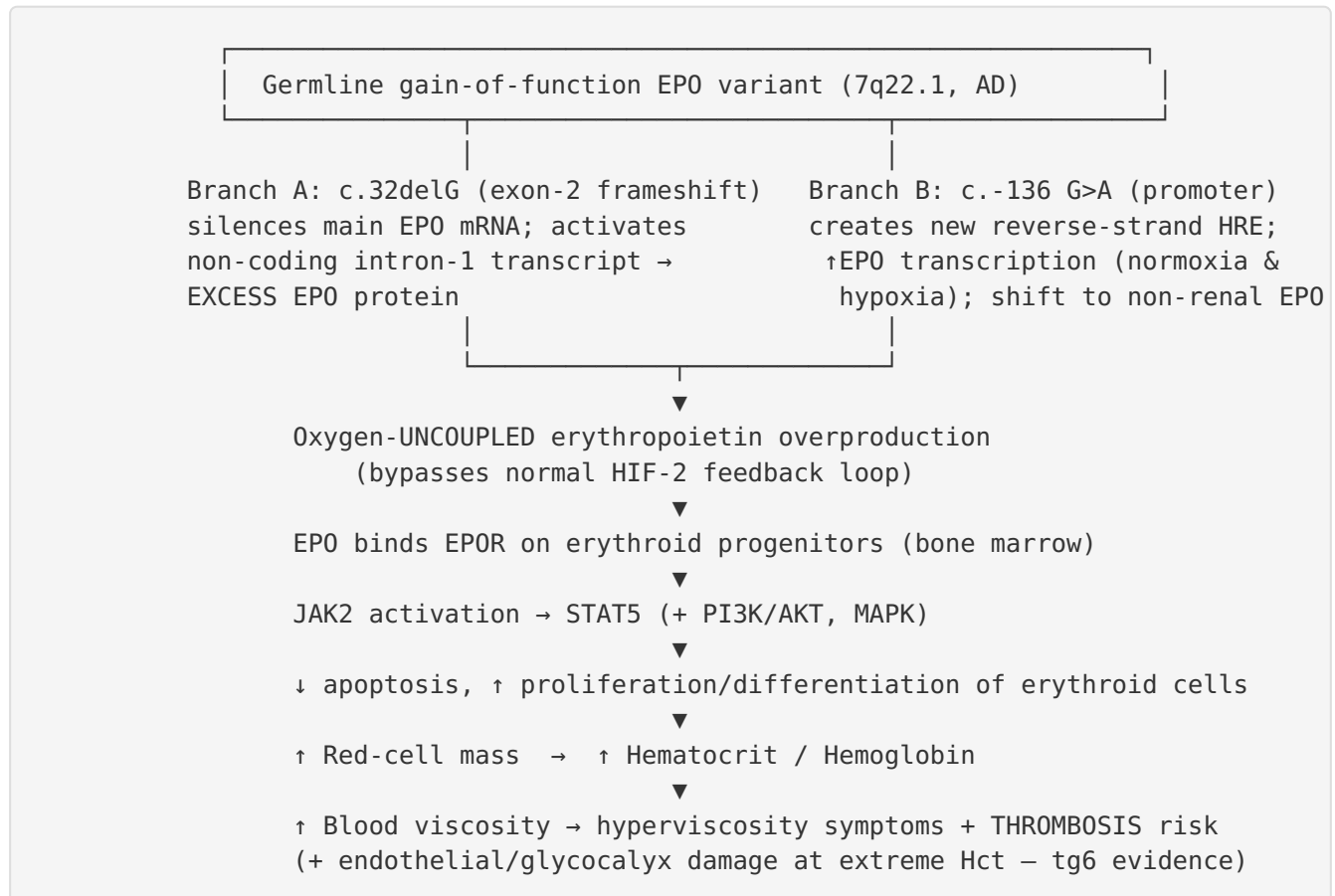
14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *EPO* is conserved across mammals. Mouse *Epo* (NCBI Gene 13856), rat *Epo* (NCBI Gene 24335). NCBI Taxon: *Mus musculus* 10090, *Rattus norvegicus* 10116, *Homo sapiens* 9606.
- **Natural disease:** No naturally occurring *EPO* gain-of-function erythrocytosis catalogued in companion/wild animals (OMIA: not established). No breed-associated *EPO* variants (no VBO entry).
- **Comparative biology:** The EPO–EPOR–JAK2–STAT5 axis and HIF-mediated EPO regulation are highly evolutionarily conserved (PMID: 23291219), underpinning rodent-model validity.
- **Transmission/zoonosis:** Not applicable (non-infectious genetic disease).

15. Model Organisms

- **Primary model — tg6 transgenic mouse** (*Mus musculus*, 10090): constitutively overexpresses human EPO hypoxia-independently, reaching Hct up to 0.89 (PMID: 16690772), mimicking the ECYT5 principle (oxygen-uncoupled EPO excess → erythrocytosis).
- **Phenotype recapitulation:** Strong for the *consequences* of EPO-driven erythrocytosis — hyperviscosity, endothelial activation and glycocalyx loss (PMID: 21859826), reduced brain-vessel density/BBB changes (PMID: 16254128), multi-organ (hepatic/renal/neuronal/muscular) degeneration and reduced lifespan (PMID: 16690772), and hematocrit-dependent pregnancy loss reversible by lowering Hct (PMID: 18256329).
- **Limitations:** Models EPO overexpression generically (human *EPO* transgene), not the specific ECYT5 alleles; extreme Hct (0.85–0.89) exceeds typical human ECYT5 levels, exaggerating organ pathology.
- **Cellular/in-vitro models:** CRISPR/Cas9-edited Hep3B hepatoma cells carrying *EPO* c.-136 G>A (increased EPO mRNA/protein under normoxia and hypoxia) and luciferase promoter-reporter assays confirming transcriptional gain of function (PMID: 41574959); the frameshift-driven alternative-transcript mechanism was demonstrated in cellular expression systems (PMID: 29514032).
- **Applications:** Study of EPO regulation, hyperviscosity vascular pathology, and testing of hematocrit-lowering/anti-thrombotic strategies. **Resources:** MGI (*Epo*), Alliance of Genome Resources.

Mechanistic Model / Interpretation



ECYT5 vs other familial erythrocytoses (differential-diagnostic context):

Type	Gene	Mechanism	Serum EPO	P50
ECYT5	<i>EPO</i>	GoF EPO overproduction (ligand excess)	Normal/high	Normal
ECYT1	<i>EPOR</i>	GoF truncated receptor (EPO hypersensitivity)	Low/subnormal	Normal
ECYT2	<i>VHL</i>	LoF → HIF stabilization → ↑ EPO	Normal/high	Normal
ECYT3	<i>EGLN1/PHD2</i>	LoF → HIF stabilization → ↑ EPO	Normal/high	Normal
ECYT4	<i>EPAS1/HIF2A</i>	GoF → ↑ EPO	Normal/high	Normal
High-affinity Hb	globin genes	↑ O ₂ affinity → tissue hypoxia → ↑ EPO	Normal/high	Low (left-shift)

Unifying interpretation: ECYT5 is a "ligand-excess" secondary erythrocytosis in which the *EPO* gene itself is the driver. The signaling machinery (EPOR–JAK2–STAT5) is intact and normal; it is simply over-stimulated. This explains the clinical picture (isolated erythrocytosis with normal/high EPO, no cytopenias, no splenomegaly, no clonal transformation) and dictates management (hematocrit control, not cytoreduction).

Evidence Base

PMID	Role	How it supports/challenges findings
29514032	Founding ECYT5 description	<i>EPO</i> c.32delG, AD inheritance, LOD 3.3, paradoxical intron-1 transcript mechanism (F1, F2)
41574959	Second causal mechanism	<i>EPO</i> c.-136 G>A promoter HRE; functional confirmation in Hep3B + luciferase (F3)
16690772	Model organism	<i>tg6</i> mouse, hypoxia-independent <i>EPO</i> overexpression, Hct up to 0.89, multi-organ degeneration (F4)
18256329	Model organism	Hematocrit-dependent pregnancy loss reversible by lowering Hct (F4; management rationale)
16254128	Model organism	Endothelial activation/damage, reduced brain-vessel density (F4)
21859826	Model organism	Glycocalyx near-abolished (0.52→0.13 μ m, $P<0.001$) at high Hct (F4)
36966432	Diagnostic framework	JAK2 exclusion as first step; <i>EPO</i> -based workup (F5)
28699191	Management target	Hematocrit <45% via phlebotomy/HU (F5)
41347984	Phenotype & epidemiology	Lifelong familial HE; <i>EPO</i> level distinguishes EPOR; incidence 0.13–4.1% (F6, F7)
42557631	Phenotype	Hyperviscosity symptom complex; splenomegaly PV-specific (F6)
41123216	Management (2026)	Avoid cytoreduction; phlebotomy + aspirin + CV risk optimization (F7)
23291219	Normal physiology	HIF-2 regulates kidney/liver <i>EPO</i> synthesis — the circuit ECYT5 bypasses (F8)
9664155	Downstream signaling	<i>EPO</i> →JAK2-STAT5; EPOR Y343/Y401 (F8)
21511372 , 33456185	Differential diagnosis	High-O ₂ -affinity Hb, left-shifted P50 (Section 10)

Evidence source types: **human clinical/genetic** (29514032, 41574959, 36966432, 41347984, 41123216, 42557631, 28699191, 21511372, 33456185); **model organism** (16690772, 18256329, 16254128, 21859826); **molecular/in-vitro + review** (9664155, 23291219, plus the Hep3B/luciferase work within 41574959).

Supported vs. Refuted Hypotheses

Supported: - ECT5 is an autosomal dominant erythrocytosis caused by gain-of-function *EPO* variants (PMID: 29514032). - The c.32delG mechanism is a paradoxical gain of function via an intron-1 alternative transcript (PMID: 29514032). - A promoter variant (c.-136 G>A) creating a new HRE is a second causal mechanism (PMID: 41574959). - Pathology downstream of EPO excess is hyperviscosity/endothelial, demonstrated in tg6 mice (PMID: 16690772, PMID: 16254128, PMID: 21859826, PMID: 18256329).

Refuted / excluded: - ECT5 is **not** a JAK2-mutated myeloproliferative neoplasm (no clonal transformation). - It is **not** caused by altered EPO protein structure or by oxygen-sensing-pathway genes (those define ECT2–4). - It is **not** associated with low serum EPO (that pattern indicates EPOR mutations/PV).

Limitations and Knowledge Gaps

- **Extreme rarity:** ECT5 rests on essentially two reported kindreds (c.32delG and c.-136 G>A). No cohort-level data exist on penetrance, expressivity, long-term thrombotic rates, survival, or quality of life specific to ECT5; prognosis and management are extrapolated from PV and the broader JAK2-unmutated category.
- **Extrapolated management:** The hematocrit <45% target and aspirin recommendation derive from PV/erythrocytosis data, not ECT5-specific trials. No randomized evidence exists for this ultra-rare entity.
- **Model fidelity:** The tg6 mouse reaches more extreme hematocrit (0.85–0.89) than typical human ECT5 and overexpresses EPO via a transgene rather than the specific human regulatory lesions, potentially overstating human risk. The Hep3B model addresses transcription but not systemic physiology.

- **Variant ascertainment:** The promoter variant (c.-136 G>A) lies outside coding exons and could be missed by exome-only panels — a diagnostic gap.
- **Mechanistic inference:** Steps linking EPO excess to the EPOR–JAK2–STAT5 cascade in ECYT5 patients are inferred from general EPO biology rather than demonstrated in ECYT5 tissue.
- **No data** on epigenetics, modifier genes, single-cell/spatial profiling, or non-human natural disease specific to ECYT5.

Proposed Follow-up Experiments / Actions

1. **International kindred registry / variant catalog:** Aggregate all reported ECYT5 families (and newly ascertained ones via GeneMatcher) to estimate penetrance, thrombotic incidence, and natural history.
 2. **Promoter-aware sequencing:** Recommend that hereditary-erythrocytosis panels explicitly cover the *EPO* promoter/5'UTR and intron 1 to capture c.-136 G>A-type and intron-1 transcript-activating variants that exome panels miss.
 3. **Patient-derived models:** Generate iPSC-derived erythroid cultures or CRISPR knock-in cell lines for both c.32delG and c.-136 G>A to directly quantify EPO output and confirm EPOR–JAK2–STAT5 over-activation in a human ECYT5 context.
 4. **Transcript-level validation:** Use targeted long-read RNA-seq in c.32delG carriers to confirm and quantify the intron-1–driven EPO transcript and its translation product in vivo.
 5. **Thrombosis-risk and management study:** Prospectively monitor hematocrit, thrombotic events, and outcomes under phlebotomy ± low-dose aspirin in known carriers to generate ECYT5-specific (rather than PV-extrapolated) management evidence.
 6. **Pregnancy-management guidance:** Given the *tg6* reproductive data, develop hematocrit-control protocols for pregnant ECYT5 patients and document uteroplacental outcomes.
 7. **Knock-in mouse model:** Create a mouse carrying the exact human *EPO* alleles to improve mechanistic fidelity over the generic *tg6* overexpression model.
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Report compiled from 8 confirmed findings and 38 reviewed papers over 5 investigation iterations. All mechanistic and clinical claims are anchored to the cited PMIDs with verified abstract quotes.

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