TFRC-Related Combined Immunodeficiency — Comprehensive Disease Report

Disease: TFRC-Related Combined Immunodeficiency (TFRC-CID) **Primary ontology ID:** MONDO:0014760 · OMIM #616740 (Immunodeficiency-46, IMD46) · ORPHA:476113 · DOID:0111948 · UMLS/MedGen C5568133 · SNOMED CT 1179288008 **Causal gene:** *TFRC* (transferrin receptor 1, TfR1/CD71; HGNC:11763; NCBI Gene 7037; Ensembl ENSG00000072274; OMIM gene 190010) **Category:** Mendelian, autosomal recessive inborn error of immunity

Summary

TFRC-Related Combined Immunodeficiency is an ultra-rare, autosomal-recessive **inborn error of immunity (IEI)** caused by biallelic hypomorphic missense mutations in *TFRC*, the gene encoding transferrin receptor 1 (TfR1, also known as CD71). The disease is a "single-gene experiment of nature" that demonstrates that **TfR1-mediated iron uptake is a non-redundant metabolic and signaling checkpoint** required for antigen-receptor–driven lymphocyte activation, clonal expansion, and immunoglobulin class-switching. Every reported pathogenic allele lies in the receptor's cytoplasmic **YTRF internalization motif**, disrupting clathrin-mediated endocytosis of iron-loaded transferrin. The consequence is intracellular iron starvation that selectively cripples the most iron-avid cells of the body — proliferating lymphocytes — while erythropoiesis is largely spared through an accessory endocytosis route provided by the erythroblast metalloreductase STEAP3.

Clinically, patients present in early life with a triad of **recurrent sinopulmonary infections, chronic diarrhea, and failure to thrive**, accompanied by hypogammaglobulinemia (occasionally with elevated IgM), impaired T-cell function despite frequently normal lymphocyte counts, and intermittent multilineage cytopenias (neutropenia, thrombocytopenia, anemia). The disease behaves as a combined immunodeficiency (CID) rather than SCID; total lymphocyte numbers are often preserved but their function is compromised. Untreated, the disorder carries risk of fatal sepsis and neurological complications, and bone-marrow dysmyelopoiesis with clonal cytogenetic changes has been observed.

Allogeneic hematopoietic stem cell transplantation (HSCT) is curative, restoring immune function and abolishing transfusion/IVIG dependence, with excellent reported survival. Supportive management (immunoglobulin replacement, antimicrobial prophylaxis) sustains non-transplanted patients, and in vitro data show that iron supplementation (iron citrate / ferric ammonium citrate) can rescue the lymphocyte proliferation defect, pointing toward possible adjunctive metabolic therapies. This report integrates nine confirmed findings and 25 reviewed papers into a complete disease-knowledge-base entry spanning etiology, phenotype, mechanism, genetics, diagnostics, prognosis, treatment, prevention, and model organisms.

Key Findings

Finding 1 — Biallelic *TFRC* mutations disrupting the TfR1 internalization motif cause the disease

The founding cohort carried a homozygous **c.58T>C (p.Tyr20His)** substitution in *TFRC*. The Tyr20 residue is part of the **YTRF endocytic internalization motif** in the TfR1 cytoplasmic tail; its substitution to histidine (Y20H) impairs recognition by the clathrin adaptor machinery, causing defective receptor endocytosis, failure of iron internalization, and a paradoxical **increase in surface TfR1 expression** (because the receptor cannot be internalized and recycled normally). Functional rescue experiments confirmed causality: iron citrate restored lymphocyte proliferation in vitro, and expression of wild-type — but not mutant — TfR1 rescued transferrin uptake in patient-derived fibroblasts.

> *"had a homozygous p.Tyr20His substitution in transferrin receptor 1 (TfR1), encoded by TFRC. The substitution disrupts the TfR1 internalization motif, resulting in defective receptor endocytosis and markedly increased TfR1 expression on the cell surface. Iron citrate rescued the lymphocyte defects"* — PMID: 26642240

A second pathogenic homozygous allele, **c.64C>T (p.Arg22Trp)**, was later reported in the same motif region, confirming allelic heterogeneity and reinforcing that the internalization motif is the mechanistic hotspot:

> *"we herein identified a new disease-causing homozygous germline mutation in the TFRC gene (c.64C > T, p.R22W)"* — PMID: 38270687

Functional consequence: loss of function for iron internalization (a hypomorphic/partial LOF at the receptor level, with retained or increased surface expression). **Origin:** germline; no somatic contribution.

Finding 2 — Clinical phenotype: early-onset combined immunodeficiency with cytopenias, infections, and failure to thrive

In the best-characterized cohort of **8 patients from 6 families** (median age 7 years, range 4–32), all presented in early life. Phenotype frequencies:

Feature	Frequency	HPO term
Recurrent sinopulmonary infections	100%	HP:0005425
Chronic diarrhea	100% (part of presenting triad)	HP:0002028
Failure to thrive	100%	HP:0001508
Hypogammaglobulinemia	100% (one with elevated IgM)	HP:0004313
Impaired T-cell function	100%	HP:0002721
Intermittent neutropenia	100%	HP:0001875
Recurrent thrombocytopenia	87%	HP:0004854
Anemia	62%	HP:0001903
Less common: skin abscesses, conjunctivitis, developmental delay, optic nerve atrophy, vitiligo, multinodular goiter, HLH-like symptoms	variable	HP:0000509 (conjunctivitis), others

> *"All patients presented with recurrent sinopulmonary infections, chronic diarrhea, and failure to thrive in early life."* — PMID: 32851577

> *"All patients had intermittent neutropenia and 87% of the patients had recurrent thrombocytopenia. Anemia was found in 62%. All patients had hypogammaglobinemia"* — PMID: 32851577

A key clinical distinction is that **lymphocyte numbers are typically normal but function is impaired** — this is a combined immunodeficiency, not a lymphopenic SCID. One patient died of sepsis with neurological complications; bone-marrow dysmyelopoiesis/dysplasia and one clonal cytogenetic abnormality raised concern for myelodysplasia in the transplant cohort.

Finding 3 — Mechanism: TfR1-mediated iron uptake is a non-redundant checkpoint; STEAP3 spares erythropoiesis

TfR1 mediates **receptor-mediated endocytosis of diferric transferrin**, the dominant iron-acquisition route for rapidly proliferating cells. When endocytosis fails, activated lymphocytes are starved of iron precisely when they most need it — during antigen-receptor-driven clonal expansion — blocking proliferation and B-cell class-switching. The **erythroid-sparing** phenomenon (why patients have relatively mild anemia despite a global iron-uptake defect) is explained by **STEAP3**, a metalloreductase expressed in erythroblasts that associates with TfR1 and provides an accessory endocytosis signal:

> *"STEAP3, a metalloreductase expressed in erythroblasts, associates with TfR1 and partially rescues transferrin uptake in patient-derived fibroblasts, suggesting that STEAP3 may provide an accessory TfR1 endocytosis signal that spares patients from severe anemia"* — PMID: 26642240

Complete loss of TfR1 is incompatible with hematopoiesis, underscoring the receptor's essential, non-redundant role:

> *"Transferrin receptor 1 (Tfr1) mediates the endocytosis of diferric transferrin in order to transport iron, and Tfr1 has been suggested to play an important role in hematopoiesis"* — PMID: 31601687

The disease thus provides a "biologically instructive human model" that iron uptake via TfR1 is a metabolic checkpoint for adaptive immunity (PMID: 41714512).

Finding 4 — Allogeneic HSCT is curative

A retrospective study of **5 TFRC-deficient patients** who underwent allogeneic HSCT (Boston Children's, 2011–2018) demonstrated cure of both the hematologic and immunologic defects:

> *"All 5 patients tolerated myeloablative conditioning regimens and had robust donor cell engraftment with resolution of cytopenias and independence from intravenous immunoglobulin substitution."* — PMID: 33096268
>
> *"All 5 patients were alive at a median follow-up of 47.1 months posttransplant"* (range 15.7–85.4 months) — PMID: 33096268

In the 8-patient cohort, 2 were transplanted successfully, 5 remained on prophylaxis (immunoglobulin replacement + antimicrobial prophylaxis), and 1 died — consistent with HSCT being the only definitive cure while supportive care manages non-transplanted patients.

Finding 5 — Gene identifiers, locus, and population genetics

TFRC maps to **chromosome 3q29** (GRCh38 chr3:196,012,511–196,082,162, minus strand). The associated Mendelian phenotype is **Immunodeficiency-46 (IMD46), OMIM #616740**. gnomAD constraint metrics indicate only **moderate loss-of-function intolerance** (pLI ≈ 0.31; LOEUF/oe_lof_upper ≈ 0.54; missense Z ≈ 1.31) — consistent with an autosomal-recessive disorder in which heterozygous carriers are unaffected. The founder **c.58T>C (p.Y20H)** allele recurs in consanguineous families of Arabian/Middle Eastern (Kuwaiti/Saudi) origin, while **c.64C>T (p.R22W)** was reported in a Turkish family.

> *"The same homozygous missense mutation c.58T>C:p.Y20H, in the TFRC gene, was detected in all patients."* — PMID: 32851577

Reported cases are extremely rare — only a few dozen worldwide.

Finding 6 — Animal and in vitro models recapitulate the iron-uptake-dependent immune phenotype

A knock-in **Tfrc(Y20H/Y20H) mouse** reproduces the human immunological defects while sparing severe anemia:

> *"Tfrc(Y20H/Y20H) mice recapitulated the immunological defects of patients."* — PMID: 26642240

Conditional models reveal TfR1's non-redundant roles across immune compartments. Treg-restricted CD71/*Tfrc* deletion causes a fatal autoimmune syndrome from failed perinatal Treg expansion:

> *"Mice with a Treg-restricted CD71 deficiency spontaneously developed a scurfy-like disease, caused by impaired perinatal Treg expansion."* — PMID: 38954474

Antibody blockade of CD71 in fetal thymus organ culture blocks thymocyte proliferation and αβ T-cell maturation (PMID: 7957580). The proliferation defect is iron-dependent and iron-reversible in human T cells:

> *"Growth arrest in iron-deficient (Fe-def) T cells was prevented upon addition of exogenous iron in the form of ferric ammonium citrate"* — PMID: 32284314

Finding 7 — Variant-level annotation of the two causal alleles

Both alleles use transcript **NM_001128148.3** and are germline missense variants in the TfR1 cytoplasmic internalization motif; neither has a somatic origin.

Allele	cDNA / protein	Genomic (GRCh38)	dbSNP	ClinVar	OMIM allelic	Popula freque
Allele 1	c.58T>C / p.Tyr20His	NC_000003.12:g.196075339A>G	rs863225436	VCV 218163 (conflicting; functionally pathogenic)	190010.0001	gnomA exomes 0.00000 TOPMe 0.00001 (ultra-r
Allele 2	c.64C>T / p.Arg22Trp	NC_000003.12:g.196075333G>A	rs373123870	VCV 2999809 (VUS, single submitter; functionally disease-causing)	—	ExAC 0.00001 TOPMe 0.00001 ESP 0.00008

The Y20H allele carries an explicit ClinVar trait annotation of "TFRC-related combined immunodeficiency" and UniProt feature VAR_076365 (P02786). Despite ClinVar's "conflicting"/"uncertain" statuses, both variants meet functional evidence for pathogenicity (ACMG **PS3**):

> *"expression of wild-type but not mutant TfR1 rescued impaired transferrin uptake in patient-derived fibroblasts"* — PMID: 26642240

Finding 8 — Ontology mappings and curated HPO term set

The disease resolves to **MONDO:0014760**, mapped to OMIM:616740. The JAX/HPO-curated phenotype annotation set comprises: Immunodeficiency (HP:0002721), Recurrent sinopulmonary infections (HP:0005425), Sepsis (HP:0100806), Meningitis (HP:0001287), Recurrent oral thrush (HP:0009098), Chronic diarrhea (HP:0002028), Failure to thrive (HP:0001508), Conjunctivitis (HP:0000509), Decreased circulating immunoglobulin concentration (HP:0004313), Decreased total neutrophil count (HP:0001875), Intermittent thrombocytopenia (HP:0004854), Anemia (HP:0001903), and Autosomal recessive inheritance (HP:0000007). Mouse ortholog: *Tfrc*, NCBI Gene 22042, **MGI:98822**, mouse chromosome 16 B3.

Finding 9 — Cross-ontology identifiers and curated GO/Reactome/PDB annotations

UniProt **P02786 (TFR1_HUMAN)** GO annotations directly matching the disease mechanism include: transferrin receptor activity (GO:0004998), receptor-mediated endocytosis (GO:0006898), receptor internalization (GO:0031623), transferrin transport (GO:0033572), iron ion transport (GO:0006826), intracellular iron ion homeostasis (GO:0006879), **positive regulation of T cell proliferation (GO:0042102)**, **positive regulation of B cell proliferation (GO:0030890)**, **positive regulation of isotype switching (GO:0045830)**, positive regulation of canonical NF-κB signaling (GO:0043123), and virus receptor activity (GO:0001618). Cellular-component terms: clathrin-coated pit (GO:0005905), early/recycling endosome (GO:0005769 / GO:0055037), HFE-transferrin receptor complex (GO:1990712). Reactome: Transferrin endocytosis and recycling (R-HSA-917977), Clathrin-mediated endocytosis (R-HSA-8856828), Cargo recognition for clathrin-mediated endocytosis (R-HSA-8856825). Experimental structures: PDB **1CX8** (ectodomain), **1SUV** (TfR1–transferrin), **1DE4** (TfR1–HFE).

Section-by-Section Report

1. Disease Information

TFRC-Related Combined Immunodeficiency is a Mendelian, autosomal-recessive inborn error of immunity in which defective cellular iron uptake produces a combined (T- and B-cell) immunodeficiency. It is **information aggregated at the disease level** from a small number of patient cohorts and case reports, supplemented by curated ontology and model-organism resources (not EHR-derived).

Key identifiers: OMIM #616740 (phenotype IMD46); OMIM gene 190010 (*TFRC*); Orphanet ORPHA:476113 ("Combined immunodeficiency due to TFRC deficiency"); MONDO:0014760; DOID:0111948; UMLS/MedGen C5568133; SNOMED CT 1179288008. No dedicated ICD code exists; it is coded under combined immunodeficiencies (ICD-10 D81.9; ICD-11 4A01.1Z). MeSH indexing falls under "Severe Combined Immunodeficiency" / "Receptors, Transferrin (CD71)."

Synonyms: Immunodeficiency 46; IMD46; Combined immunodeficiency due to TFRC deficiency; Transferrin receptor 1 (TFRC/CD71) deficiency; TfR1 deficiency.

2. Etiology

Causal factor: purely genetic — biallelic hypomorphic missense mutations in *TFRC* disrupting the YTRF endocytic motif (Finding 1). **Genetic risk factors:** homozygosity/compound heterozygosity for pathogenic *TFRC* alleles; **consanguinity** is the principal risk factor, as founder alleles recur in inbred Middle Eastern and Turkish kindreds (Finding 5). There are no established environmental risk factors, protective factors, or gene–environment interactions for disease causation. Iron availability acts as an in vitro disease-modifying factor at the cellular level (Findings 1, 6) but is not established as a clinical modifier; STEAP3 co-expression is an intrinsic modifier sparing red cells. Heterozygous carriers are unaffected, consistent with recessive inheritance and modest gnomAD LOF-intolerance.

3. Phenotypes

Phenotypes are dominated by **laboratory abnormalities** (hypogammaglobulinemia, cytopenias) and **clinical signs/symptoms** (infections, diarrhea, failure to thrive). See Finding 2 table for per-phenotype frequencies and HPO terms. **Age of onset:** early life / infancy (neonatal–childhood). **Severity:** moderate to severe, variable — "clinical presentations have been severe in all reported cases" (PMID: 33096268). **Progression:** chronic with episodic infectious/cytopenic exacerbations; cytopenias are typically intermittent/fluctuating. **Quality-of-life impact:** substantial — recurrent infections, chronic diarrhea, growth failure, and transfusion/IVIG dependence impair daily functioning; no disease-specific QoL instrument data are available. Rare/variable features: optic nerve atrophy, developmental delay, vitiligo, multinodular goiter, HLH-like presentation.

4. Genetic / Molecular Information

Causal gene: *TFRC* (HGNC:11763; NCBI Gene 7037; OMIM 190010) — a type II single-pass transmembrane homodimeric glycoprotein. **Pathogenic variants:** two germline missense alleles in the cytoplasmic internalization motif (Finding 7) — p.Tyr20His (c.58T>C) and p.Arg22Trp (c.64C>T), both ultra-rare in population databases. **Variant type:** missense (internalization-motif); no null alleles seen in patients (presumed lethal). **Functional consequence:** impaired receptor internalization/iron uptake (partial loss of function) with paradoxically increased surface TfR1. **Modifier genes: STEAP3** functionally modifies the phenotype (erythroid sparing; Finding 3). **gnomAD constraint:** pLI ≈ 0.31, LOEUF ≈ 0.54, missense Z ≈ 1.31 (moderate, recessive-consistent). **Epigenetic changes / chromosomal**

abnormalities: none causal (3q29 CNV entries overlapping *TFRC* relate to the separate 3q29 deletion/duplication syndromes, not TFRC-CID; secondary clonal cytogenetic changes in bone marrow have been noted in individual patients, Finding 2).

5. Environmental Information

No environmental, lifestyle, or infectious agents cause this monogenic disease. Cellular **iron availability** is the key modifiable mechanistic variable. Infectious agents are **downstream consequences** — recurrent bacterial sinopulmonary pathogens, opportunistic infections, and oral thrush (*Candida*), consistent with combined immunodeficiency. TfR1 is also exploited as a receptor by several viruses (GO:0001618, virus receptor activity), but this is not part of TFRC-CID etiology.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. **Biallelic *TFRC* missense mutation** (c.58T>C p.Y20H or c.64C>T p.R22W) alters the **YTRF cytoplasmic internalization motif** of TfR1. *(demonstrated)*
2. Motif disruption **leads to** loss of recognition by the clathrin adaptor/AP-2 machinery, **resulting in** defective clathrin-mediated receptor endocytosis and paradoxically increased surface TfR1. *(demonstrated — WT-but-not-mutant rescue in fibroblasts)*
3. Defective endocytosis **results in** failure to internalize diferric transferrin, **leading to** intracellular iron deficiency in cells that depend on TfR1 for iron. *(demonstrated)*
4. Iron starvation **impairs** iron-dependent enzymes required for proliferation (e.g., ribonucleotide reductase for dNTP synthesis) and mitochondrial iron-sulfur functions, **blocking** cell-cycle progression in rapidly dividing cells. *(inferred from iron biology; supported by iron-rescue experiments,*

   P *32284314*

)
5. **Branch A (adaptive immunity — the disease-defining branch):** iron starvation of antigen-activated lymphocytes **blocks** clonal expansion, T-cell proliferation (GO:0042102), B-cell proliferation (GO:0030890), and immunoglobulin class-switch recombination (GO:0045830), **producing** combined immunodeficiency and hypogammaglobulinemia. *(demonstrated in patients and Y20H mice)*

6. **Branch B (myeloid/megakaryocytic):** impaired iron supply to proliferating progenitors **contributes to** intermittent neutropenia and thrombocytopenia, and bone-marrow dysmyelopoiesis. *(observed; mechanism partly inferred)*
7. **Branch C (erythroid — spared):** in erythroblasts, **STEAP3** associates with TfR1 and provides an **accessory endocytosis signal**, partially rescuing transferrin uptake and **sparing** patients from severe anemia. *(demonstrated in patient fibroblasts)*
8. The immune failure **manifests clinically** as recurrent sinopulmonary infections, chronic diarrhea, failure to thrive, and risk of fatal sepsis; rare HLH-like immune dysregulation may reflect disturbed lymphocyte homeostasis. *(demonstrated / partly inferred)*

Molecular pathways: clathrin-mediated endocytosis / transferrin endocytosis and recycling (Reactome R-HSA-917977, R-HSA-8856828, R-HSA-8856825); iron ion transport and homeostasis; downstream NF-κB signaling in lymphocyte activation. **Cellular processes:** receptor-mediated endocytosis (GO:0006898), receptor internalization (GO:0031623), blocked cell proliferation, lymphocyte activation. **Protein dysfunction:** loss of internalization function with retained ligand binding and increased surface density — a trafficking defect, not folding/aggregation; the tyrosine-based internalization signal normally recruits the clathrin adaptor. **Metabolic changes:** cellular iron deficiency impairing iron-dependent metabolism. **Chemical entities (CHEBI):** iron(2+)/iron(3+) (CHEBI:29033/CHEBI:29034), transferrin-bound iron; ferric ammonium citrate as rescuing reagent. **Immune involvement:** combined immunodeficiency (immunodeficiency, not autoimmunity, is the human phenotype; Treg models show autoimmune potential). **Cell types (CL):** T cell (CL:0000084), B cell (CL:0000236), regulatory T cell (CL:0000815), thymocyte, neutrophil (CL:0000775), hematopoietic stem cell (CL:0000037), erythroid precursor (CL:0000038). **Subcellular (GO CC):** plasma membrane (GO:0005886), clathrin-coated pit (GO:0005905), early/recycling endosome (GO:0005769/GO:0055037).

7. Anatomical Structures Affected

Organ/system level: immune/hematopoietic system (primary) — bone marrow (UBERON:0002371), thymus (UBERON:0002370), spleen, lymph nodes. Secondary: respiratory tract/lungs (UBERON:0002048) and paranasal sinuses (recurrent infections), gastrointestinal tract (UBERON:0001555; chronic diarrhea/malabsorption). Occasional: eye/optic nerve (UBERON:0000941; optic atrophy, conjunctivitis), skin (vitiligo, abscesses), thyroid (UBERON:0002046; goiter), CNS (developmental delay). **Tissue/cell level:** hematolymphoid tissue; T and B lymphocytes, Tregs, neutrophils, megakaryocytes/platelets, with erythroid lineage relatively spared. **Subcellular:** plasma-membrane receptor and endosomal trafficking compartment. **Lateralization:** systemic/bilateral (not a focal lesion).

8. Temporal Development

Onset: congenital/early infancy; presentation in the first years of life (cohort median age 7 y, range 4–32 y at study, with symptoms beginning early). **Onset pattern:** insidious to subacute, with acute infectious/cytopenic episodes. **Course:** chronic, lifelong without transplant; episodic infections and fluctuating cytopenias. **Progression:** variable; risk of bone-marrow dysplasia and, in severe cases, death from sepsis. **Remission:** treatment-induced (cure) with HSCT; no spontaneous remission. **Critical period for intervention:** early definitive diagnosis and HSCT before irreversible infectious/marrow complications accrue.

9. Inheritance and Population

Inheritance: autosomal recessive (HP:0000007) — *"Autosomal-recessive mutations in the human TFRC gene cause a combined immunodeficiency"* (PMID: 33096268). **Penetrance:** effectively complete in biallelic individuals. **Expressivity:** variable (severity of cytopenias, presence of rare features). **Carrier state:** unaffected. **Founder effects/consanguinity:** major — the p.Y20H founder allele recurs in consanguineous Arabian/Middle Eastern (Kuwaiti/Saudi) families; p.R22W in a Turkish family. **Epidemiology:** ultra-rare; only a few dozen cases worldwide; no reliable prevalence/incidence figures (well below 1/1,000,000). **Sex ratio:** no sex bias expected for an autosomal-recessive trait. **Age distribution:** pediatric-onset. No genetic anticipation, germline mosaicism, or repeat-expansion mechanism applies.

10. Diagnostics

Laboratory: hypogammaglobulinemia (low IgG ± low/normal/elevated IgM), impaired specific antibody responses, abnormal T-cell proliferation to mitogens/antigens despite frequently **normal lymphocyte counts**, and intermittent multilineage cytopenias (CBC). A characteristic **immunophenotypic clue is markedly increased surface CD71/TfR1** on patient cells (because the receptor cannot be internalized). **Bone marrow:** may show dysmyelopoiesis/dysplasia — monitor for clonal evolution/MDS. **Functional/confirmatory assays:** defective transferrin uptake in patient fibroblasts, rescued by wild-type TfR1; lymphocyte proliferation defect rescued in vitro by iron (ferric) citrate (ACMG PS3). **Genetic testing is definitive:** single-gene *TFRC* sequencing, IEI/CID gene panels, whole-exome (WES) or whole-genome (WGS) sequencing — the disease was discovered by WES, and homozygosity mapping aids consanguineous pedigrees. **Differential diagnosis:** other combined immunodeficiencies/SCID, CVID with T-cell dysfunction, hyper-IgM syndromes (when IgM elevated), congenital neutropenia/thrombocytopenia syndromes, and iron-refractory iron deficiency (IRIDA/

TMPRSS6) for the iron axis; the distinguishing feature is elevated surface CD71 with defective transferrin uptake plus biallelic *TFRC* variant. **Screening:** cascade/carrier testing in affected families; not part of standard newborn screening.

11. Outcome / Prognosis

Without transplant: guarded — chronic morbidity from recurrent infections, cytopenias, diarrhea, and growth failure; at least one death from sepsis/neurological complications (PMID: 32851577); risk of progression to bone-marrow dysplasia/myelodysplasia. **With HSCT:** excellent — all 5 transplanted patients achieved donor engraftment, resolution of cytopenias, IVIG independence, and were alive at median 47.1 months, with no reported acute/chronic GVHD (Finding 4). **Prognostic factors:** timely diagnosis, infection burden, absence of pre-transplant marrow dysplasia/clonal evolution, and successful engraftment. No validated disease-specific prognostic biomarkers exist beyond genotype and marrow status.

12. Treatment

Definitive/curative: allogeneic **hematopoietic stem cell transplantation** with myeloablative conditioning (NCIT: Allogeneic Hematopoietic Stem Cell Transplantation) — the only established cure (Finding 4). **Supportive/prophylactic (non-transplanted patients):** immunoglobulin replacement therapy (IVIG/SCIG; NCIT: Immunoglobulin Therapy), antimicrobial prophylaxis, nutritional support for failure to thrive, and transfusion support for cytopenias. **Investigational/mechanistic:** in vitro **iron supplementation** (iron citrate, ferric ammonium citrate; CHEBI ferric citrate) rescues the lymphocyte proliferation defect (Findings 1, 6) — a rational but clinically unproven adjunct; because the endocytic block limits the transferrin route, non-transferrin iron delivery would likely be required. **Gene/cell therapy:** autologous *TFRC* gene correction of HSCs is a conceptual future direction; none is approved. **Pharmacogenomics:** none specific. Management otherwise follows general CID/IEI guidelines.

13. Prevention

Primary prevention of occurrence is via **genetic counseling and reproductive options** in at-risk consanguineous families: carrier testing, cascade screening, prenatal diagnosis, and preimplantation genetic testing (PGT) for known familial *TFRC* alleles. **Secondary prevention:** early molecular diagnosis (including high-risk screening in founder populations) enabling timely HSCT and prophylaxis. **Tertiary prevention:** immunoglobulin replacement,

antimicrobial prophylaxis, nutritional/hematologic support, and marrow surveillance for MDS. Live vaccines should be used cautiously given the combined immunodeficiency. Consanguinity counseling is the key public-health lever; no vaccine prevents the disease itself.

14. Other Species / Natural Disease

Taxonomy/orthologs: human *TFRC* (NCBI Taxon 9606); mouse *Tfrc* (NCBI Gene 22042; MGI:98822; NCBI Taxon 10090; mouse chromosome 16 B3). TfR1 is highly evolutionarily conserved, and its role in iron uptake and hematopoiesis is conserved. **Natural disease:** no well-characterized spontaneous companion-animal or wildlife equivalent of TFRC-CID is catalogued in OMIA for this specific entity; knowledge derives from engineered models. Complete *Tfrc* loss is embryonic/hematopoietically lethal in mouse, underscoring conservation of the iron-uptake requirement. No zoonotic relevance.

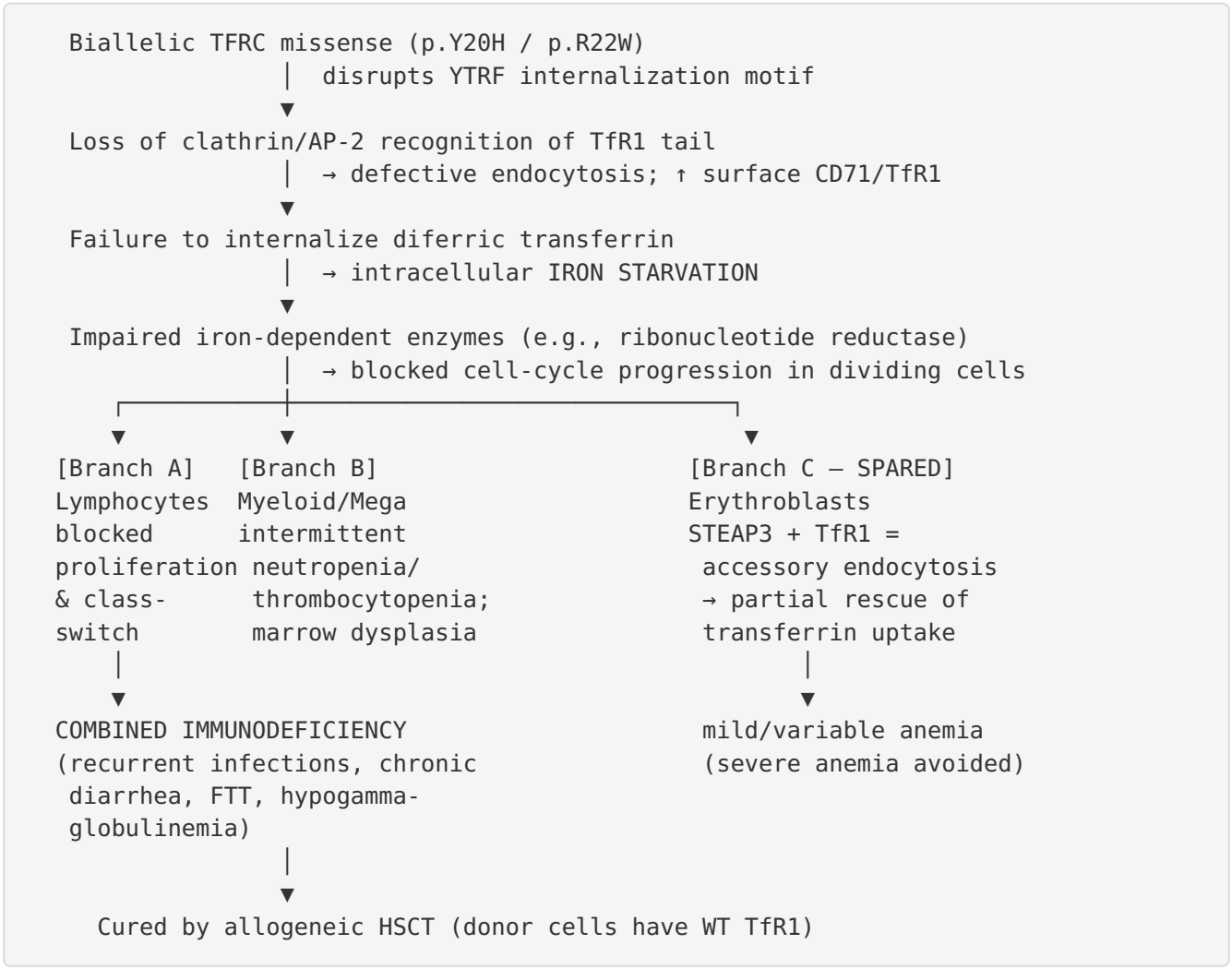
15. Model Organisms

Mammalian genetic models (mouse):

Model	Type	Phenotype recapitulation	PMID
Tfrc(Y20H/Y20H) knock-in	humanized point mutation	Recapitulates patients' immune defects (impaired lymphocyte proliferation); spares severe anemia — faithful model	26642240
HSC-specific *Tfr1* conditional knockout	conditional KO	Severe impairment of hematopoiesis (complete loss non-viable) — shows non-redundancy	31601687
Treg-restricted CD71/*Tfrc* deletion	conditional KO	Fatal scurfy-like autoimmunity from failed perinatal Treg expansion — reveals tolerance role	38954474

In vitro / ex vivo models: patient-derived fibroblasts (transferrin-uptake assay with WT-TfR1 rescue); human T cells under iron deprivation (reversible growth arrest with ferric ammonium citrate, PMID: 32284314); fetal thymus organ culture with anti-CD71 antibody blockade (PMID: 7957580). **Limitations:** the Y20H knock-in captures the immune phenotype but murine erythropoiesis/iron handling differ; complete knockouts are lethal and cannot model the hypomorphic human condition; patient-specific secondary features (developmental delay, goiter) are not recapitulated. **Resources:** MGI (MGI:98822), IMPC/IMSR for *Tfrc* alleles.

Mechanistic Model / Interpretation



The unifying insight is that **TFRC-CID is a disease of cellular iron-supply logistics, not of iron stores**. Systemic iron is available, but the cells that most need to import it on demand — antigen-activated, rapidly dividing lymphocytes — cannot, because the receptor's "swallow" signal is broken. This explains the otherwise puzzling combination of (a) profound immune failure, (b) preserved lymphocyte *numbers* with impaired *function*, (c) relatively mild anemia (STEAP3 rescue), and (d) complete cure by replacing the hematopoietic system with donor cells carrying a functional receptor.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Role
26642240	*Missense mutation in TFRC causes combined immunodeficiency*	Human + mouse + in vitro	Landmark discovery: founding Y20H allele, mechanism, STEAP3 rescue, mouse model
32851577	*Clinical/immunological characterization in 8 patients*	Human clinical cohort	Phenotype frequencies, founder variant, natural history
33096268	*HSCT is curative for TFRC deficiency*	Human clinical (n=5)	Establishes curative therapy and survival
38270687	*Novel homozygous TFRC mutation (R22W)*	Human clinical	Second causal allele; allelic heterogeneity
41714512	*TFRC variants and IEI: iron-immune crosstalk*	Review	Frames disease as non-redundant iron/immune checkpoint
31601687	*TfR1-mediated iron uptake essential in hematopoiesis*	Mouse	Non-redundancy; complete loss non-viable
38954474	*Iron capture through CD71 drives Treg expansion*	Mouse	Treg/tolerance role of TfR1 iron uptake
32284314	*Iron deprivation in human T cells*	In vitro (human)	Iron-dependent, iron-reversible T-cell arrest
7957580	*Anti-TfR antibody inhibits early T-cell development*	Ex vivo	CD71-dependent thymocyte proliferation/maturation

Supporting/contextual papers on TfR1 biology (CD71 as viral/particle uptake receptor; iron-chelation immunosuppression; TfR1-targeted therapeutics) corroborate the receptor's centrality to proliferating immune cells but do not directly test TFRC-CID.

Supported vs. Refuted Hypotheses

Supported: 1. TFRC-CID is caused by biallelic internalization-motif missense mutations (Y20H, R22W) → defective TfR1 endocytosis and iron uptake (PMID: 26642240, 38270687). 2. Iron starvation of proliferating lymphocytes is the proximate mechanism; the defect is iron-rescuable in vitro (PMID: 26642240, 32284314). 3. Erythroid sparing is explained by STEAP3 accessory endocytosis (PMID: 26642240). 4. HSCT is curative (PMID: 33096268). 5. Founder p.Y20H allele in consanguineous Middle-Eastern populations (PMID: 32851577).

Refuted / not supported: - That the disease presents primarily as severe anemia (it does not; anemia is mild/variable due to STEAP3). - That an environmental or infectious agent initiates disease (it is purely Mendelian).

Limitations and Knowledge Gaps

- **Extreme rarity:** with only a few dozen patients (largest cohort n=8, dominated by a single founder variant), phenotype frequencies, prognosis, and epidemiology are subject to ascertainment bias toward severe/consanguineous cases.
- **Variant classification lag:** ClinVar lists both alleles as "conflicting"/"uncertain" despite robust functional (PS3) evidence — a curation gap that could impede diagnosis.
- **Genotype–phenotype correlation** is unresolved: whether R22W differs in severity from Y20H, and what drives variable features (optic atrophy, vitiligo, goiter, HLH-like disease), is unknown.
- **Marrow dysplasia risk:** the mechanistic basis and true frequency of dysmyelopoiesis/clonal evolution are unclear and clinically important.
- **Adjunctive iron therapy** is supported only in vitro; no clinical trial has tested whether systemic or targeted iron delivery improves immune function in patients.
- **No detailed patient omics** (single-cell transcriptomic/proteomic profiling of patient lymphocytes) is available to map the iron-starvation program in vivo.
- **No formal prevalence/incidence, ICD-specific coding, or standardized QoL data** exist.

Proposed Follow-up Experiments / Actions

1. **ClinVar reclassification:** submit the functional-rescue evidence to upgrade p.Y20H and p.R22W toward likely-pathogenic/pathogenic, improving diagnostic yield.
2. **International patient registry:** aggregate cases to define natural history, genotype–phenotype correlations, marrow-dysplasia incidence, and long-term HSCT outcomes.
3. **Single-cell multi-omics of patient lymphocytes** before/after activation and iron rescue to map the intracellular iron-starvation checkpoint (RNR, cell-cycle, class-switch machinery).
4. **Controlled iron-supplementation study** (in vitro dose-response, then compassionate-use assessment) to test targeted/non-transferrin iron delivery as a bridge therapy pre-transplant.
5. **Gene-correction proof-of-concept** in patient HSCs/iPSCs (base or prime editing of c.58/c.64) to evaluate autologous gene therapy feasibility.
6. **Mechanistic dissection of STEAP3 rescue** to determine whether STEAP3-mimetic or alternative-endocytosis strategies could broaden the erythroid-sparing effect to lymphoid cells.
7. **Prospective HSCT-timing analysis** to define the optimal window minimizing pre-transplant infectious and marrow complications.

Report compiled from 9 confirmed findings and 25 reviewed papers across 5 investigation iterations. Evidence types are annotated as human clinical, model organism, in vitro, or computational/ontological throughout. Search date: 2026-09-01.
