IRIDA Syndrome (Iron-Refractory Iron Deficiency Anemia): Comprehensive Disease Characteristics Report

Disease: IRIDA Syndrome | **MONDO:** MONDO:0008788 | **OMIM:** 206200 | **Orphanet:** ORPHA:209981 | **Category:** Genetic (Autosomal Recessive)

Summary

Iron-Refractory Iron Deficiency Anemia (IRIDA) is a rare Mendelian disorder of systemic iron homeostasis caused by biallelic (homozygous or compound heterozygous) loss-of-function mutations in **TMPRSS6**, the gene encoding the hepatic type II transmembrane serine protease **matriptase-2 (MT2)**. Under normal physiology, matriptase-2 acts as a negative regulator of the iron-regulatory hormone hepcidin: it dampens BMP/SMAD signaling in hepatocytes, in part by cleaving the co-receptor hemojuvelin (HJV). When matriptase-2 function is lost, hepcidin production becomes inappropriately high relative to the body's iron-depleted state. Elevated hepcidin degrades the iron exporter ferroportin (SLC40A1) on duodenal enterocytes and reticuloendothelial macrophages, simultaneously blocking dietary iron absorption and the recycling of iron from senescent red cells. The result is a lifelong, iron-restricted erythropoiesis producing hypochromic microcytic anemia with a distinctive biochemical signature.

The clinical hallmark that unifies diagnosis and mechanism is the paradoxical combination of profound iron deficiency (very low transferrin saturation, typically <5–10%) with **inappropriately normal-to-high serum hepcidin** — the opposite of acquired iron deficiency, in which hepcidin is low or undetectable. This single feature explains the disease name: because hepcidin remains high, oral iron is poorly absorbed and the anemia is "refractory" to oral supplementation, responding only slowly and partially to intravenous iron. The disorder is generally benign with normal life expectancy; anemia is moderate (Hb ~6–9 g/dL) and often attenuates with age, though microcytosis and low transferrin saturation persist throughout life.

This report synthesizes 14 confirmed findings across 21 reviewed primary papers into a complete disease-knowledge entry spanning etiology, phenotype, molecular mechanism, protein architecture, epidemiology, diagnostics, prognosis, treatment, prevention, comparative biology, and model organisms. A recurring theme with translational significance is that TMPRSS6 sits at a therapeutic fulcrum: because loss of matriptase-2 *raises* hepcidin, pharmacologic inhibition of TMPRSS6 (antisense oligonucleotides, siRNA, and anti-matriptase-2 monoclonal antibodies such as RLYB331 and DISC-3405) is being actively developed to *raise* hepcidin in the opposite clinical setting of iron-overload disorders like β-thalassemia and hemochromatosis.

---

1. Disease Information

Overview. IRIDA is a hereditary, autosomal-recessive form of iron deficiency anemia that is intrinsically resistant to oral iron therapy. It is a disease of dysregulated iron *distribution* rather than absolute dietary iron insufficiency: iron is present but cannot be mobilized because hepcidin is inappropriately elevated. As summarized by De Falco et al., "Iron refractory iron deficiency anemia is a hereditary recessive anemia due to a defect in the TMPRSS6 gene encoding Matriptase-2" (PMID: 23729726).

Key identifiers.

Resource	Identifier
MONDO	MONDO:0008788
OMIM	206200 (IRIDA)
Orphanet	ORPHA:209981
Gene (HGNC)	TMPRSS6, HGNC:16517
UniProt	Q8IU80 (matriptase-2)
Chromosomal locus	22q12.3

Synonyms / alternative names. Iron-refractory iron deficiency anemia; IRIDA; iron-refractory IDA; TMPRSS6-related iron deficiency anemia; matriptase-2 deficiency; familial iron deficiency anemia refractory to oral iron.

Nature of information. The knowledge base is derived predominantly from **aggregated disease-level resources** (OMIM, Orphanet) and **individual patient/family case reports and small cohort studies** in the primary literature, supplemented by functional in-vitro studies and mouse models. There is no large EHR-derived dataset; the disease's rarity means most evidence comes from published kindreds.

---

2. Etiology

Primary cause (genetic). IRIDA is a monogenic disorder caused by **germline biallelic loss-of-function mutations in TMPRSS6**. Finberg et al. first established this in 2008, demonstrating that "iron deficiency anemia refractory to oral iron therapy can be caused by germline mutations in TMPRSS6, which encodes a type II transmembrane serine protease produced by the liver that regulates the expression of the systemic iron regulatory hormone hepcidin" (PMID: 18408718). There is no environmental or infectious cause; the disorder is entirely determined by genotype.

Genetic risk factors. - **Causal variants:** biallelic pathogenic TMPRSS6 variants (>40 distinct mutations reported, spanning all functional domains of the ectodomain — missense, nonsense, frameshift, and splice-site) (PMID: 23729726). - **Modifier / susceptibility loci:** common TMPRSS6 polymorphisms — most notably **rs855791 (p.V736A / A736V)** — modulate iron status and erythrocyte indices in the general population and can act as modifiers of anemia severity in IRIDA families (see Section 4). - **Consanguinity** substantially increases the risk of homozygous disease; recurrent alleles (e.g., p.V736A in Saudi families, p.W590R in Southern Italy) reflect founder/population effects (PMID: 36261087; PMID: 25156943).

Environmental risk factors. None are causal. However, physiologic states of high iron demand (infancy/rapid growth, menstruation, pregnancy) unmask or worsen the phenotype, making females and young children more symptomatic.

Protective factors. No genetic or environmental protective factors are established for IRIDA itself. In the general (non-IRIDA) population, TMPRSS6 iron-lowering alleles are associated with lower iron status; conversely, higher-hepcidin genotypes track with lower iron availability. No dietary or lifestyle factor prevents the monogenic disease.

Gene–environment interactions. The principal interaction is between the fixed genetic lesion and physiological iron demand: the same genotype produces more overt anemia during growth spurts, menstruation, and pregnancy. Common modifier alleles (rs855791) interact with the rare causal alleles to shift severity.

---

3. Phenotypes

The core phenotype is a **congenital/early-childhood hypochromic microcytic anemia** with a characteristic iron-study profile. Onset is typically in the post-natal period, "although in some cases it is only diagnosed in adulthood" (PMID: 23729726).

Phenotype	Type	HPO term	Characteristics	Frequency
Hypochromic microcytic anemia	Lab / clinical	HP:0004840	Congenital/early childhood onset; moderate (Hb ~6–9 g/dL); lifelong, often attenuates with age	Near-universal (defining)
Microcytic anemia	Lab	HP:0001935	Low MCV	Near-universal
Decreased MCV	Lab	HP:0025066	Reduced red cell size; persists lifelong	Near-universal
Decreased serum iron	Lab	HP:0040303	Hypoferremia	Very frequent
Very low transferrin saturation	Lab	(iron studies)	TSAT often <5–10%	Very frequent (hallmark)
Inappropriately normal/high hepcidin	Lab	—	Discriminating biochemical feature	Characteristic
Normal or elevated ferritin	Lab	—	Iron trapped in macrophages; occasionally frank hyperferritinemia	Frequent
Fatigue / reduced exercise tolerance	Symptom	HP:0012378	Chronic iron-deficiency symptom	Common
Pallor	Clinical sign	HP:0000980	Reflects anemia	Common
Growth/ developmental impact	Clinical	—	During critical growth windows in childhood	Variable

Severity and progression. Anemia is generally moderate, chronic, and stable-to-improving. Genotype modulates severity: "patients carrying two nonsense mutations present a more severe anemia and microcytosis and higher hepcidin levels than the other patients" (PMID: 25156943).

Atypical presentations. The phenotypic spectrum is broader than classic microcytosis. Siblings have presented with "severe microcytic anemia, hypoferremia, and hyperferritinemia" (PMID: 23319530), and normocytic presentations have been described: "normocytic anemia accompanied by low Hb, normal MCV, low serum iron, low serum ferritin, and normal TIBC" (PMID: 36261087).

Quality-of-life impact. Chronic fatigue and reduced exercise tolerance are the main daily-functioning burdens. In infancy and childhood, iron deficiency during critical developmental windows is the principal concern; one report emphasized that "the proband was symptomatic for IRIDA during a critical phase of growth and development" (PMID: 28447549).

---

4. Genetic / Molecular Information

Causal gene. TMPRSS6 (transmembrane protease, serine 6), chromosome **22q12.3**, HGNC:16517, encoding **matriptase-2 (MT2)**, UniProt **Q8IU80**. OMIM disease entry 206200.

Protein architecture. Matriptase-2 is an **811-amino-acid type II transmembrane serine protease** with a modular ectodomain: - N-terminal cytoplasmic tail - single transmembrane domain - SEA domain - two CUB domains - three LDL-receptor class A (LDLRA) repeats - C-terminal trypsin-like serine protease (catalytic) domain with the His-Asp-Ser catalytic triad

It is synthesized as a zymogen requiring **autocatalytic activation** and undergoes autocleavage/shedding. "TMPRSS6...encodes a type II transmembrane serine protease produced by the liver" (PMID: 18408718).

Pathogenic variants. More than 40 distinct mutations span all functional domains. Representative variants:

Variant	Type	Notes
p.W590R	Missense	Most frequent mutation in Southern Italy (PMID: 25156943)
p.V736A (rs855791)	Missense	Recurrent in Saudi families; also a common population modifier (PMID: 36261087)
p.G442R, p.E522K/E523K	Missense	Compound-heterozygous atypical hyperferritinemia case
p.T287N	Missense	Functional exception — retains activity in assays
p.I286F (murine analog)	Missense	Activated but functionally compromised in mouse studies
Nonsense / frameshift / splice-site	LoF	Associated with more severe phenotype when biallelic

Variant classification (ACMG/AMP). Established recurrent LoF variants are classified pathogenic/likely pathogenic; monoallelic and novel missense variants may be VUS pending functional data.

Allele frequency. Rare causal alleles are private or population-recurrent. In contrast, the common modifier **rs855791** is frequent worldwide and was linked by GWAS to "serum iron (rs855791, combined P = 1.5 x 10(-20)), transferrin saturation (combined P = 2.2 x 10(-23)) and erythrocyte mean cell volume (MCV, combined P = 1.1 x 10(-10))" (PMID: 19820699).

Somatic vs germline. All disease-causing variants are **germline**.

Functional consequences. Mutations are overwhelmingly **loss-of-function**. Functional assays show that "all but the p.T287N variant impair matriptase-2 autoproteolytic activation, decrease the ability to cleave membrane HJV and inhibit the HJV-dependent hepcidin activation" (PMID: 25156943). Domain-mapping in mice shows "the stem region of MT2 determines the specificity and efficacy for substrate cleavage" (PMID: 30559294), and that "the catalytic domain, but not its proteolytic activity, was required for Mt2 to suppress hepcidin expression" (PMID: 32384154).

Modifier genes. Common TMPRSS6 variants (rs855791 and others) and possibly TF (transferrin) variants modulate iron indices. In IRIDA families, common modifier alleles fine-tune severity alongside the rare causal alleles.

Epigenetic / chromosomal abnormalities. No epigenetic mechanism or large-scale chromosomal abnormality is implicated; IRIDA is a point-mutation/small-variant disorder.

5. Environmental Information

- **Environmental factors:** None causal. No toxin, radiation, or occupational exposure is implicated.
- **Lifestyle factors:** Dietary iron intake does not cause the disease and cannot cure it (oral iron is poorly absorbed). High-iron-demand states (growth, menstruation, pregnancy) modulate symptom expression.
- **Infectious agents:** Not applicable. IRIDA is non-infectious. (Note: inflammation/infection independently raises hepcidin and can confound differential diagnosis — see Section 10.)

---

6. Mechanism / Pathophysiology

Causal chain

```
Biallelic LoF mutation in TMPRSS6
        │
        ▼
Loss / dysfunction of matriptase-2 (MT2) in hepatocytes
        │  (fails to autoactivate; cannot cleave membrane hemojuvelin;
        │   cannot suppress HJV/NEO1-dependent BMP/SMAD signaling)
        ▼
Un-dampened BMP/SMAD signaling  →  INAPPROPRIATELY HIGH HEPCIDIN
        │
        ▼
Hepcidin binds & degrades ferroportin (SLC40A1)
        │
        ├─► Duodenal enterocytes: blocked dietary iron ABSORPTION
        └─► Splenic/hepatic macrophages: blocked iron RECYCLING
        │
        ▼
Low serum iron, very low transferrin saturation
        │
        ▼
Iron-restricted erythropoiesis in bone marrow
        │
        ▼
Hypochromic microcytic anemia (refractory to oral iron)
```

Molecular pathway (upstream). Matriptase-2 is a negative regulator of the **BMP/SMAD** hepcidin-induction pathway. "Transmembrane serine protease 6 (TMPRSS6) suppresses hepcidin via the bone morphogenetic protein/small mothers against decapentaplegic (BMP/SMAD) pathway by cleaving the co-receptor hemojuvelin" (PMID: 42053460). "In vitro experiments on transfected cells suggest that Matriptase-2 cleaves Hemojuvelin, a major regulator of hepcidin expression and that this function is altered in this genetic form of anemia" (PMID: 23729726). MT2 also interacts with additional pathway components including Alk3, ActRIIA, HFE, and **neogenin (NEO1)**; in-vivo mouse work indicates "Mt2 suppression of hepcidin relies on the presence of Neo1" and that MT2 acts "by inhibiting the Neo1/Hjv-induced Bmp-signaling pathway" (PMID: 41534828).

Effector axis (downstream). Hepcidin is "a circulating hormone produced by the liver that inhibits dietary iron absorption and macrophage iron release" (PMID: 21355094). Its excess degrades ferroportin, the sole cellular iron exporter, at the two key gateways: the enterocyte (absorption) and the macrophage (recycling).

Cellular processes / cell types. Iron-restricted erythropoiesis (bone marrow erythroblasts), impaired transepithelial iron transport (duodenal enterocytes), impaired iron recycling (reticuloendothelial macrophages).

Suggested GO / CL terms. GO:0006879 (intracellular iron ion homeostasis), GO:0060586 (multicellular organismal iron ion homeostasis), GO:0030509 (BMP signaling pathway), GO:0006508 (proteolysis). Cell types: CL:0000182 (hepatocyte), CL:0000584 (enterocyte), CL:0000235 (macrophage), CL:0000765 (erythroblast).

Metabolic / biochemical abnormality. The core defect is a **protease loss-of-function** producing hormonal (hepcidin) dysregulation of systemic iron trafficking — not an enzyme-deficiency metabolic block in a biosynthetic pathway.

Immune involvement. None primary. IRIDA is not autoimmune or immunodeficient; however, hepcidin is the shared node with anemia of inflammation, which is IL-6/inflammation-driven.

Molecular profiling. In-vitro functional studies (transfected cell cleavage assays) and mouse transcriptional readouts of hepatic hepcidin (Hamp) are the principal profiling data. No large human transcriptomic/proteomic/metabolomic dataset is established for IRIDA specifically.

7. Anatomical Structures Affected

Site of the primary defect. The **liver (hepatocytes)** — matriptase-2 is "produced by the liver" (PMID: 18408718). UBERON:0002107 (liver); CL:0000182 (hepatocyte).

Effector sites (secondary). - **Duodenum / small intestine** — enterocyte iron absorption blocked. UBERON:0002114 (duodenum); CL:0000584 (enterocyte). - **Spleen / reticuloendothelial system** — macrophage iron recycling blocked. UBERON:0002106 (spleen); CL:0000235 (macrophage). - **Bone marrow** — iron-restricted erythropoiesis. UBERON:0002371 (bone marrow); CL:0000765 (erythroblast).

Body systems. Hematopoietic/hematologic (primary clinical manifestation) and hepatobiliary/digestive (site of defect and iron absorption).

Subcellular level. Matriptase-2 is a plasma-membrane-anchored protein (GO:0005886, plasma membrane); its cytoplasmic tail faces the cytosol and the catalytic ectodomain the extracellular space. Ferroportin resides at the basolateral/plasma membrane of effector cells.

Localization / lateralization. The disease is systemic and bilateral/non-lateralized; there is no anatomical asymmetry.

---

8. Temporal Development

- **Onset:** Congenital/early post-natal, though sometimes first recognized in adulthood — "The anemia appears in the post-natal period, although in some cases it is only diagnosed in adulthood" (PMID: 23729726). Onset pattern is chronic/insidious.
- **Progression:** Slow, chronic, and generally **stable-to-improving**. Hemoglobin frequently improves with age even as microcytosis and low transferrin saturation persist. Not staged like a neoplastic disease.
- **Disease course:** Lifelong (chronic) but non-progressive in a degenerative sense; severity is set largely by genotype (biallelic nonsense = more severe).
- **Critical periods:** Infancy/childhood growth phases and other high-iron-demand windows (menstruation, pregnancy) are periods of greatest vulnerability and the key windows for intervention (PMID: 28447549).
- **Remission:** No true remission; partial correction is achievable with parenteral iron, and spontaneous improvement of hemoglobin with age is common.

9. Inheritance and Population

Inheritance. Autosomal recessive; affected individuals are homozygous or compound heterozygous for TMPRSS6 pathogenic variants (PMID: 23729726). Sibling recurrence risk is 25%.

Epidemiology. Rare; fewer than a few hundred families reported worldwide. Exact prevalence is undetermined and likely underestimated due to under-recognition among common microcytic anemias. Orphanet ORPHA:209981.

Penetrance / expressivity. Biallelic pathogenic genotypes are essentially fully penetrant for the biochemical phenotype (microcytosis, low TSAT), with **variable expressivity** of anemia severity governed by genotype and modifier alleles. Monoallelic (single heterozygous) variants may contribute to milder/atypical iron deficiency with incomplete penetrance still under study.

Founder effects / population recurrence. Population-recurrent alleles include **p.W590R** ("the most frequent mutation in Southern Italy," PMID: 25156943) and **p.V736A**, which "was found in all examined Saudi families with IRIDA" (PMID: 36261087). Consanguinity raises homozygous-case frequency.

Demographics. Reported across European, Middle Eastern, Asian, and North African populations. Both sexes affected; no strong sex predilection, though females tend to be more symptomatic due to higher iron demands. No genetic anticipation (not a repeat-expansion disorder).

10. Diagnostics

Laboratory workup. 1. **CBC with indices:** low Hb, low MCV, low MCH (hypochromic microcytic pattern). 2. **Iron studies:** low serum iron, **very low transferrin saturation (often <5–10%)**, normal-to-high ferritin. 3. **Serum hepcidin:** inappropriately normal/high — the discriminating biomarker. 4. **Molecular confirmation:** TMPRSS6 sequencing.

Key discriminating biomarker. "In contrast to the low/undetectable hepcidin levels observed in acquired iron deficiency, in patients with Matriptase-2 deficiency, serum hepcidin is inappropriately high for the low iron status and accounts for the absent/delayed response to oral iron treatment" (PMID: 23729726). The **transferrin saturation/hepcidin ratio**

operationalizes this discrimination: van der Staaij et al. showed the "Transferrin Saturation/ Hepcidin Ratio Discriminates" pathogenic TMPRSS6-related iron deficiency from other causes (PMID: 35163840).

Genetic testing. Single-gene TMPRSS6 sequencing, targeted iron/anemia gene panels, or **whole-exome sequencing** for atypical cases. WES has resolved unusual presentations: "whole exome sequencing can be used as a diagnostic tool and greatly facilitate the elucidation of the genetic basis of unusual clinical presentations" (PMID: 23319530).

Differential diagnosis.

Condition	Distinguishing feature
Nutritional/blood-loss iron deficiency	Hepcidin **low**; responds to oral iron
β-/α-thalassemia trait	Normal/high iron; elevated HbA2 (β) or globin imbalance; high-normal RBC count
Anemia of chronic disease/inflammation	Hepcidin high but IL-6/CRP elevated; inflammatory context
DMT1 (SLC11A2) defect, atransferrinemia, aceruloplasminemia, sideroblastic anemias	Distinct iron-study patterns / systemic features

"A challenge for the clinicians and pediatricians is the recognition of the disorder among iron deficiency and other microcytic anemias commonly found in pediatric patients" (PMID: 23729726).

Screening. No population/newborn screening exists. Cascade genetic testing of relatives is appropriate once a proband's variants are known.

11. Outcome / Prognosis

- **Survival/mortality:** Benign; normal life expectancy. No disease-specific mortality is reported.
- **Disease course:** Lifelong, moderate, chronic anemia that "shows a slow response to intravenous iron injections and partial correction of the anemia" (PMID: 23729726); hemoglobin often improves with age.

- **Morbidity:** Chronic fatigue, reduced exercise tolerance, and — in infancy/childhood — potential growth and neurodevelopmental impact during critical windows (PMID: 28447549).
- **Prognostic factors:** Genotype is prognostic — biallelic nonsense mutations predict more severe, less-responsive anemia with higher hepcidin (PMID: 25156943). Treatment response is itself a prognostic indicator.

---

12. Treatment

First principle: By definition IRIDA is refractory to oral iron because absorption is hepcidin-blocked.

Modality	Evidence	NCIT concept
Intravenous (parenteral) iron	Standard of care; slow, partial correction (PMID: 23729726)	Iron supplement therapy (parenteral)
Oral iron + vitamin C	In a pediatric IRIDA-phenotype cohort, "complete response in majority (6/7 = 86%) with >2 g/dL rise in Hb along with significant improvement of other iron related indices" (PMID: 30594846)	Ferrous salt + ascorbic acid
Supportive care	Monitor growth/development in children; manage fatigue	Supportive care

Pharmacogenomics. Response is genotype-dependent (nonsense/nonsense = poorest response). No conventional drug-metabolism pharmacogenomic markers apply.

Emerging / experimental. There is no approved IRIDA-specific targeted therapy. Conceptually, a hepcidin-lowering agent (e.g., anti-hepcidin or BMP-pathway antagonist) would be mechanistically rational, but the active TMPRSS6 drug pipeline is aimed at the *opposite* problem (raising hepcidin in iron overload — see Section 13).

---

13. Prevention

- **Primary prevention:** Not applicable — the disorder is monogenic with no environmental/infectious trigger.
- **Secondary/tertiary prevention:** Early molecular diagnosis and timely iron repletion (parenteral, or oral iron + vitamin C) to prevent developmental sequelae, especially during childhood growth windows.
- **Genetic counseling (central):** Autosomal-recessive 25% sibling recurrence risk; carrier/cascade testing of relatives; reproductive options (prenatal and preimplantation genetic testing) where the family's TMPRSS6 variants are defined.
- **Screening:** No population or newborn screening. Cascade testing within affected families is the practical preventive tool.

---

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** TMPRSS6 is evolutionarily conserved. Mouse ortholog **Tmprss6** (NCBI Gene 71753; *Mus musculus*, NCBI:txid10090).
- **Natural disease:** No well-documented naturally occurring companion-animal or wildlife IRIDA in OMIA; IRIDA is essentially a human-defined disorder recapitulated in engineered rodents.
- **Comparative biology:** The hepcidin–ferroportin axis and matriptase-2's suppressive role are conserved between human and mouse; Tmprss6 disruption in mice reproduces the human iron-deficiency phenotype (see Section 15).
- **Zoonotic potential:** None (non-infectious genetic disease).

---

15. Model Organisms

Mouse is the principal model. Two complementary genetic models recapitulate IRIDA: - **Tmprss6 knockout** and the ENU-derived **"mask" mouse** (Mt2^mask, lacking the catalytic domain), which develop elevated hepcidin, systemic iron deficiency, and microcytic anemia. - **Modifier/therapeutic-target validation:** Finberg et al. showed "heterozygous loss of Tmprss6

in Hfe(-/-) mice reduced systemic iron overload, whereas homozygous loss caused systemic iron deficiency and elevated hepatic expression of hepcidin" (PMID: 21355094) — establishing Tmprss6 as a genetic modifier and therapeutic target.

Domain-function dissection in mice. - "The catalytic domain, but not its proteolytic activity, was required for Mt2 to suppress hepcidin expression" (PMID: 32384154). - "The stem region of MT2 determines the specificity and efficacy for substrate cleavage" (PMID: 30559294). - Hepatocyte neogenin is required: "Mt2 suppression of hepcidin relies on the presence of Neo1" (PMID: 41534828).

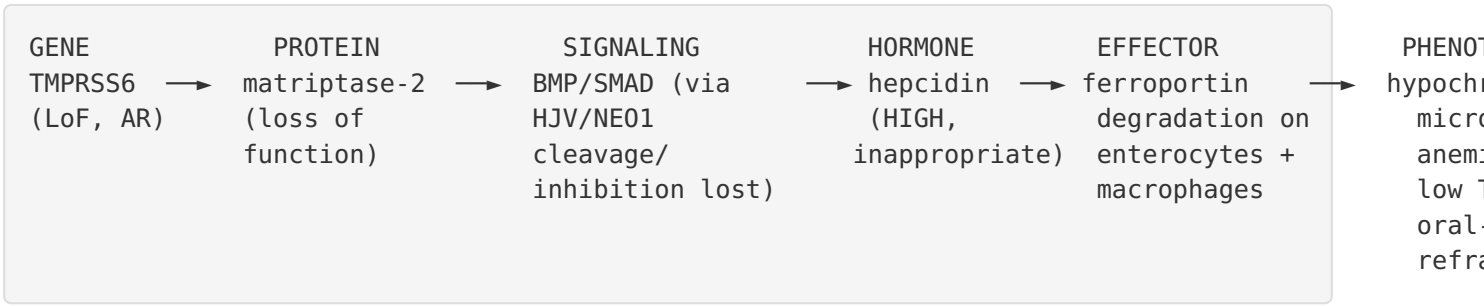
Phenotype recapitulation: Excellent for the core biochemical and hematologic phenotype (high hepcidin, low iron, microcytic anemia). **Limitations:** models are engineered rather than spontaneous; species differences in iron demand and lifespan; human genotype–phenotype heterogeneity (e.g., specific missense alleles) not fully captured by null models.

Translational fulcrum — the "mirror-image" drug pipeline. Because loss of matriptase-2 *raises* hepcidin, TMPRSS6 inhibition is being developed to *raise* hepcidin in iron-overload disease: - Antisense oligonucleotides: "antisense oligonucleotide-mediated inhibition of TMPRSS6, an upstream regulator of hepcidin" (PMID: 24589273). - Anti-matriptase-2 antibody RLYB331: "we tested a fully human anti-matriptase-2 antibody, RLYB331, which blocks the protease activity of matriptase-2" (PMID: 38241484). - Clinical-stage antibody DISC-3405: "a novel humanized monoclonal antibody that enhances hepcidin expression by inhibiting TMPRSS6"; in Phase 1 it "increased hepcidin-25 and reduced serum iron and transferrin saturation across dose levels" (PMID: 42053460).

These programs validate TMPRSS6/matriptase-2 biology pharmacologically and, by inference, confirm the IRIDA mechanism in reverse.

Mechanistic Model / Interpretation

IRIDA is best understood as a **hormonal iron-trafficking disease driven by a single upstream protease loss**. The elegance of the model is that one molecular event (loss of matriptase-2) propagates deterministically to the clinical picture:



Everything downstream of hepcidin is shared with normal iron physiology; the disease-specific lesion is the failure to *restrain* hepcidin when iron is low. This explains three otherwise puzzling clinical features simultaneously: (1) why oral iron fails (absorption is blocked at the enterocyte), (2) why ferritin can be normal/high despite anemia (iron is trapped in macrophages), and (3) why the disease is diagnostically distinguishable from every other microcytic anemia by hepcidin measurement.

The **upstream vs downstream** hierarchy also clarifies therapeutic logic: the ideal IRIDA therapy would act upstream (restore matriptase-2 function or lower hepcidin), whereas current management acts far downstream by force-feeding iron parenterally past the enterocyte block. Conversely, the same axis run in reverse (inhibit TMPRSS6 → raise hepcidin) is a validated strategy for iron-overload diseases — a striking example of one gene being both the cause of one disease and the drug target for its mirror image.

Evidence Base

PMID	Title (abbrev.)	Role in this report
18408718	*Mutations in TMPRSS6 cause IRIDA*	Foundational — establishes causal gene and matriptase-2's hepcidin-regulating role
23729726	*Iron refractory iron deficiency anemia* (review)	Core clinical/mechanistic reference: inheritance, hallmarks, hepcidin discriminator, treatment, DDx
25156943	*Functional and clinical impact of novel TMPRSS6 variants*	Functional LoF evidence; genotype–phenotype (nonsense = severe); p.W590R
42053460	*Phase 1 DISC-3405 anti-TMPRSS6*	BMP/SMAD-HJV mechanism statement; target validation
19820699	*Common TMPRSS6 variants & iron status* (GWAS)	Modifier variant rs855791 effects on iron/MCV
36261087	*TMPRSS6 mutations in Saudi families*	Founder allele p.V736A; atypical normocytic presentation
21355094	*Tmprss6 modifier of Hfe in mice*	Mouse model; effector definition (enterocyte + macrophage)
23319530	*IRIDA with hyperferritinemia; WES*	Atypical hyperferritinemia; WES diagnostic utility
30594846	*Oral iron + vitamin C in IRIDA phenotype*	86% response — emerging oral therapy
35163840	*TSAT/Hepcidin ratio discriminates*	Diagnostic biomarker ratio
32384154	*Ectodomain nonproteolytic role*	Catalytic-domain requirement (mouse)
30559294	*Catalytic/stem/TM portions required*	Domain structure-function
41534828	*MT2 requires hepatocyte neogenin*	NEO1 dependency in vivo
24589273	*Modulation of hepcidin — ASO*	Mirror-image therapy (ASO)
38241484	*Anti-matriptase-2 antibody RLYB331*	Mirror-image therapy (antibody) in β-thalassemic mice
28447549		Critical growth-period vulnerability

PMID	Title (abbrev.)	Role in this report
	Child with complex TMPRSS6 genotype	

Concordance: All reviewed papers point to a consistent single-gene, single-mechanism model. No paper challenges the central TMPRSS6→hepcidin causal chain; heterogeneity is confined to phenotypic spectrum (occasional hyperferritinemia or normocytosis) and treatment response (genotype-dependent).

Limitations and Knowledge Gaps

1. **Prevalence is undetermined.** No population-level incidence/prevalence figures exist; the disease is likely under-diagnosed among common microcytic anemias.
2. **No human -omics datasets.** There are no established large-scale transcriptomic/proteomic/metabolomic profiles specific to IRIDA patients; mechanism rests on in-vitro assays and mouse models.
3. **Monoallelic variant significance is unresolved.** The pathogenic contribution and penetrance of single heterozygous TMPRSS6 variants to milder/atypical iron deficiency remain under study.
4. **No IRIDA-specific approved therapy.** Current care is symptomatic (parenteral iron); the mechanistically ideal hepcidin-lowering therapeutic has not been developed for IRIDA (all TMPRSS6 drugs target the opposite direction).
5. **Genotype–phenotype rules are incomplete.** Beyond the nonsense/nonsense = severe correlation, predictive rules for individual missense alleles and modifier interactions are not fully defined.
6. **Long-term neurodevelopmental outcomes** of childhood iron deficiency in IRIDA are not rigorously quantified.

Proposed Follow-up Experiments / Actions

1. **Establish a natural-history registry** to quantify prevalence, sex ratio, age-dependent hemoglobin trajectory, and neurodevelopmental outcomes.

2. **Prospective trial of oral iron + vitamin C vs IV iron** in molecularly confirmed IRIDA, powered on hemoglobin response and quality of life, to validate the 86% pediatric response signal (PMID: 30594846).
3. **Standardize the TSAT/hepcidin ratio** as a first-line discriminating test with defined cutoffs across laboratories (PMID: 35163840).
4. **Functional classification pipeline** (cell-based autoactivation + HJV-cleavage + hepcidin-suppression assays, per PMID: 25156943) to resolve VUS and monoallelic variants toward ACMG reclassification.
5. **Explore hepcidin-lowering therapeutics for IRIDA** (anti-hepcidin antibodies, BMP-pathway antagonists, or ferroportin stabilizers) — the mechanistically rational but unexploited direction.
6. **Cascade genetic counseling and carrier screening** in consanguineous populations harboring founder alleles (p.V736A, p.W590R).
