

Glutathione Reductase Deficiency: A Comprehensive Disease Characteristics Report

Disease: Glutathione Reductase Deficiency (hereditary) **MONDO ID:** MONDO:0019531 **OMIM:** 618660 (Hemolytic anemia due to glutathione reductase deficiency) **Gene:** *GSR* (HGNC:4623), chromosome 8p12 **Category:** Mendelian, autosomal recessive **Report date:** 2026-10-15

Summary

Glutathione reductase (GR) deficiency exists in **two biologically distinct forms that must not be conflated**. The first and overwhelmingly more common form is an **acquired, riboflavin-responsive partial deficiency**: because GR requires FAD (derived from dietary riboflavin/vitamin B2) as a cofactor, dietary riboflavin insufficiency lowers measured GR activity. This form is reversible with riboflavin supplementation, affects a substantial fraction of some populations (~20–25% partial deficiency in a Saudi cohort), and is clinically benign. The second form — the subject of this report and the entity catalogued under MONDO:0019531 — is a **rare, hereditary, autosomal recessive enzymopathy** caused by biallelic loss-of-function mutations in the *GSR* gene. This hereditary form is **irreversible** (not corrected by riboflavin or FAD) and is extraordinarily rare: only 2 cases were found among >15,000 blood samples screened.

Mechanistically, *GSR* encodes a homodimeric, FAD-dependent, NADPH-disulfide oxidoreductase (EC 1.8.1.7; UniProt P00390) that regenerates reduced glutathione (GSH) from oxidized glutathione disulfide (GSSG). Loss of this recycling capacity cripples the GSH-dependent antioxidant defense of erythrocytes and the ocular lens, producing the clinical triad of **oxidant-triggered (favism) hemolytic anemia, cataracts, and neonatal jaundice**. Critically, the phenotype is usually **mild and episodic rather than chronic**, because a parallel, evolutionarily conserved **thioredoxin/thioredoxin-reductase (Trx/TrxR) system** partially compensates for the loss of GSSG reduction. This buffering is reflected in population genetics: *GSR* is completely loss-of-function tolerant in gnomAD ($pLI \approx 0$), predicting a biallelic frequency near 1 in 4 million — consistent with the near-absence of hereditary cases in population screens.

Management is limited to **oxidant-trigger avoidance (fava beans, oxidant drugs, infection-related oxidative stress) and supportive transfusion during hemolytic crises**, mirroring the paradigm established for G6PD deficiency. There is no disease-specific pharmacotherapy, and riboflavin does not help the hereditary form. Prognosis is favorable, with described enzyme-null individuals surviving to adulthood with only episodic, trigger-related hemolysis. A striking inversion of the disease biology is that GSR has been identified as the *top cellular suppressor of ferroptosis*, making the very function lost in this deficiency an exploitable vulnerability in oncology.

Key Findings

Finding 1 — Hereditary GR deficiency is an ultra-rare autosomal recessive disorder caused by biallelic *GSR* loss-of-function mutations

Hereditary GR deficiency is defined molecularly by biallelic loss-of-function variants in *GSR* on chromosome 8p12 (also mapped to 8p21.2 in cytogenetic deletion reports). Its rarity is well documented: Kamerbeek and colleagues found hereditary GR deficiency in **only 2 cases when testing more than 15,000 blood samples** (PMID: 17185460).

The molecular lesions span the classic loss-of-function spectrum. In one family (presenting with favism and cataract), patients carried a **homozygous 2,246-bp deletion** such that "translated GR is expected to lack almost the complete dimerization domain, which results in unstable and inactive enzyme" (PMID: 17185460). A second, novel patient presenting with severe neonatal jaundice was a **compound heterozygote**, "with a premature stop codon on one allele and a substitution of glycine 330, a highly conserved residue in the superfamily of NAD(P)H-dependent disulfide reductases, into alanine on the other allele" (PMID: 17185460). The Gly330Ala substitution drastically impairs thermostability.

The autosomal recessive inheritance was established decades earlier in the landmark consanguineous family of Loos et al., where "a virtually complete absence of glutathione reductase activity was found in the erythrocytes of all three children (one male, two females) from a consanguineous marriage" (PMID: 947404), with intermediate parental enzyme values — the classic signature of recessive inheritance.

Finding 2 — Clinical phenotype: favism-triggered hemolysis, cataracts, and neonatal jaundice

The clinical spectrum is narrow and oxidative-stress-related. In the classic family, "clinically, this deficiency was manifested by hemolytic crises after eating fava beans in the eldest daughter (patient), and possibly by cataracts in her own and in her brother's eyes" (PMID: 947404). The novel compound-heterozygous patient presented "with severe neonatal jaundice" (PMID: 17185460).

The diagnostic hallmark is oxidative instability of erythrocyte glutathione: "severely diminished glutathione stability during incubation with acetylphenylhydrazine was observed in the erythrocytes of the siblings" (PMID: 947404), with intermediate values in the obligate-carrier parents. Importantly, leukocytes are also affected (PMN ~8%, lymphocytes ~4%, monocytes ~15% of normal GR activity), reflecting the ubiquitous expression of the enzyme.

Suggested HPO terms: Hemolytic anemia (HP:0001878), Hemolytic anemia with episodic crises, Cataract (HP:0000518), Neonatal hyperbilirubinemia/Neonatal jaundice (HP:0006579), Jaundice (HP:0000952), Reticulocytosis (HP:0001923).

Finding 3 — Two distinct forms: common acquired (riboflavin-responsive) vs. rare irreversible hereditary

This distinction is central to the disease entity and to its diagnosis. In 1,691 Saudi individuals, "the overall frequency of partial GR deficiency was 24.5% and 20.3% in males and females respectively. In addition, 17.8% of males and 22.4% of females suffered from GR deficiency due to riboflavin deficiency. This could be easily corrected by dietary supplementation with riboflavin. **No cases of severe GR deficiency were identified**" (PMID: 11924113).

By contrast, the hereditary form is refractory: "the enzyme activity could not be restored either by addition of FAD in vitro or by administration of riboflavin in vivo" (PMID: 947404). The dependence of GR on FAD is also the basis of the **erythrocyte glutathione reductase activation coefficient (EGRAC)**, the standard functional biomarker of riboflavin/vitamin B2 status.

Feature	Acquired (riboflavin-responsive)	Hereditary (<i>GSR</i> mutation)
Cause	Dietary riboflavin/FAD deficiency	Biallelic <i>GSR</i> LoF variants
Frequency	Common (~20–25% partial in some populations)	Ultra-rare (2 / >15,000)
FAD/riboflavin response	Corrects deficiency (EGRAC normalizes)	No response
Enzyme protein	Present	Absent or unstable
Clinical impact	Benign	Episodic hemolysis, cataract, jaundice
Inheritance	Nutritional	Autosomal recessive

Finding 4 — *GSR* supports neutrophil host defense (model organisms)

Beyond erythrocytes, *GSR* is required for phagocyte function. In *Gsr*-null mice, "*Gsr*-deficient neutrophils displayed a very transient oxidative burst that abruptly ceased shortly after stimulation" and "*Gsr*-null mice exhibited enhanced susceptibility to *Escherichia coli* challenge, indicated by dramatically increased bacterial burden, cytokine storm, striking histological abnormalities, and substantially elevated mortality" (PMID: 22279102). *GSR* also promotes fungal clearance (systemic *Candida*) and neutrophil extracellular trap (NET) formation. The human correlate appears in the Loos family, where patient neutrophils showed abnormal oxygen consumption after zymosan phagocytosis — though clinically significant immunodeficiency is **not** a prominent feature of the human hereditary disease, again pointing to compensation. Notably, "*Gsr* deficiency resulted in increased activities of cytosolic thioredoxin and thioredoxin [reductase]" in mouse cochlea (PMID: 28686716), where the thioredoxin system fully compensates.

Finding 5 — *GSR* is a homodimeric FAD/NADPH-disulfide oxidoreductase with a defined catalytic cycle

Human GR (EC 1.8.1.7; UniProt P00390) transfers electrons $\text{NADPH} \rightarrow \text{FAD} \rightarrow \text{active-site redox-active disulfide} \rightarrow \text{GSSG}$, regenerating 2 GSH. Near-atomic synchrotron cryocrystallography (1.1–0.95 Å) showed that "the bound NADPH and redox-active disulfide are positioned optimally on opposite sides of the flavin for a 1,2-addition across a flavin double bond" and

that "compression in the active site causes overlapping van der Waals radii and distortion in the nicotinamide ring of the NADPH substrate, which enhances catalysis via stereoelectronic effects" (PMID: 18638483).

Pathogenic variants act by destabilizing this fold: the 2,246-bp deletion removes most of the **dimerization domain**, preventing the functional dimer, while Gly330Ala impairs thermostability (PMID: 17185460). GR belongs to the NAD(P)H-dependent disulfide reductase (Pyr_redox / class-I pyridine nucleotide-disulfide oxidoreductase) superfamily.

Suggested GO terms: glutathione-disulfide reductase activity (GO:0004362), flavin adenine dinucleotide binding (GO:0050660), NADP binding (GO:0050661), cell redox homeostasis (GO:0045454), glutathione metabolic process (GO:0006749). **CHEBI:** glutathione (CHEBI:16856), glutathione disulfide (CHEBI:17858), NADPH (CHEBI:16474), FAD (CHEBI:16238).

Finding 6 — Pathophysiology: loss of NADPH→GSH recycling impairs antioxidant defense, causing oxidant-triggered hemolysis and cataract

In erythrocytes, NADPH from the oxidative pentose phosphate pathway (PPP) is the principal reductant; GR uses it to regenerate GSH, which — via glutathione peroxidase and in parallel with catalase — detoxifies H₂O₂ and organic/lipid peroxides. When an enzyme deficiency limits NADPH/GSH supply, "distinct membrane alterations result causing a removal of the damaged cells by the monocyte-macrophage system" (PMID: 8813716). GR deficiency sits among the rare inborn RBC antioxidant defects: "NADPH is the main source of reduction equivalents in RBCs... When NADPH becomes limiting, red cells are prone to being damaged" (PMID: 24316370).

The cataract phenotype reflects a parallel mechanism in the lens: "human cataractous lenses showed decreased activities of glutathione reductase, glutathione peroxidase... superoxide dismutase" with GSH depletion and lipid peroxidation (PMID: 1737065).

Finding 7 — Management is supportive; the hereditary form is generally mild with favorable prognosis

No disease-specific pharmacotherapy exists. Because the hereditary form is riboflavin/FAD-unresponsive (PMID: 947404), management parallels other oxidant-triggered RBC enzymopathies such as G6PD deficiency: a "G6PD-deficient patient... lacks the ability to protect red blood cells against oxidative stresses from certain drugs, metabolic conditions, infections, and ingestion of fava beans" (PMID: 19769422) — the same oxidant-avoidance paradigm applies here. Prognosis is favorable because "the amount of reduced glutathione in the

erythrocytes was normal in each case" ([PMID: 947404](#)) at baseline, explaining the absence of chronic hemolysis between oxidant challenges, consistent with thioredoxin-system compensation ([PMID: 28686716](#)).

Finding 8 — *GSR* is loss-of-function tolerant in gnomAD, predicting ~1 in 4 million biallelic births

gnomAD v4 constraint for *GSR* (ENSG00000104687, chr8:30,678,066–30,727,846, GRCh38) shows $pLI \approx 1.8 \times 10^{-14}$ (completely LoF-tolerant), observed/expected LoF = 48/56.5 (oe_lof = 0.85, 90% CI 0.67–1.08), LoF Z = 0.96 — no depletion of truncating variants. Across 4,174 variants, 203 high-confidence predicted-LoF variants summed to an allele frequency $\approx 4.9 \times 10^{-4}$, giving a heterozygous carrier frequency $\approx 0.10\%$ (~1 in 1,000) and a predicted biallelic frequency (q^2) $\approx 2.4 \times 10^{-7}$ (~1 in 4 million). The two most common stop-gained alleles lie at the extreme 3' end of the gene, likely truncating only terminal residues, so the true pathogenic-carrier rate is even lower — consistent with "only 2 cases when testing more than 15,000 blood samples" ([PMID: 17185460](#)).

Finding 9 — Thioredoxin backup for GSSG reduction is evolutionarily conserved, explaining the mild phenotype

The mildness of the phenotype is explained by a conserved alternative GSSG-reducing system. In *Saccharomyces cerevisiae*, cells lacking GLR1 (the GSSG-reductase ortholog) survive, and "the thioredoxin-thioredoxin reductase system can function as an alternative system" to reduce GSSG in vivo ([PMID: 19951944](#)). Overexpressing TRX1/TRX2 lowers GSSG; deleting them in *glr1* cells raises it. Glr1 "has been shown to colocalize to the cytoplasm and mitochondria" ([PMID: 15701801](#)), relevant to compartment-specific redox roles. This mirrors mammalian data (mouse cochlea, [PMID: 28686716](#)). **Orthologs:** mouse *Gsr* (NCBI Gene 14782), *S. cerevisiae* GLR1 (YPL091W).

Finding 10 — Diagnosis rests on the erythrocyte GR assay ($\pm$ FAD), EGRAC, and *GSR* sequencing

The diagnostic workup comprises: (1) a red-cell GR activity assay measuring NADPH-dependent GSSG reduction, performed **with and without added FAD** — hereditary deficiency is low and FAD-unresponsive, whereas acquired riboflavin deficiency normalizes; the EGRAC is "the functional biomarker... considered to be the gold standard index" of riboflavin status ([PMID: 27170501](#)); (2) protein detection by Western blot — "the GR protein was undetectable by Western blotting" in the enzyme-null family ([PMID: 17185460](#)); (3) molecular confirmation by

GSR sequencing/deletion analysis; (4) functional glutathione-stability testing (acetylphenylhydrazine). In riboflavin-deficiency assessment, "samples with AC $\geq$ 1.3 were considered riboflavin-deficient" (PMID: 11924113). **Differential diagnosis:** G6PD deficiency and other hereditary non-spherocytic hemolytic anemias (glutathione synthesis defects, pyruvate kinase deficiency), distinguished by their specific enzyme assays.

Finding 11 — GSR is a top suppressor of ferroptosis — the disease biology in reverse

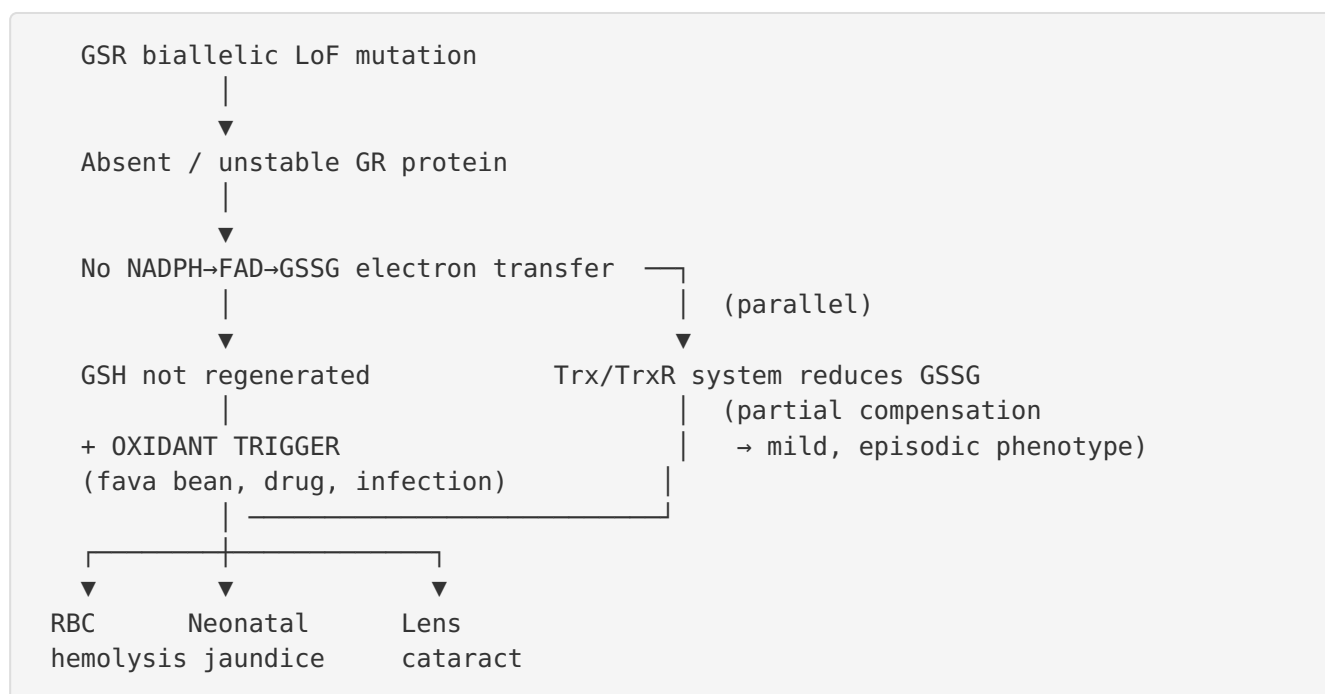
A genome-wide CRISPR-knockout screen identified that "glutathione reductase (GSR), a central enzyme maintaining reduced glutathione (GSH) homeostasis, was identified as the top suppressor of ferroptosis" and "GSR knockout or pharmacological inhibition markedly sensitized diverse cancer cell lines to RSL3-induced ferroptosis, while GSR overexpression conferred resistance" (PMID: 42681644). This positions the GSH-regenerating function lost in the deficiency as an exploitable cancer vulnerability, and is consistent with the synthetic-lethal dependence of low-GSR cancers on the thioredoxin system.

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic GSR loss-of-function mutation** (2,246-bp deletion removing the dimerization domain; nonsense allele; Gly330Ala destabilizing missense) **leads to** absent or unstable GR protein (demonstrated: undetectable by Western blot; PMID: 17185460).
2. Loss of functional homodimeric GR **results in** inability to transfer electrons from NADPH via FAD to reduce GSSG → GSH (demonstrated enzymatically; PMID: 947404).
3. Impaired GSH regeneration **leads to** a diminished capacity to buffer acute oxidative loads, although baseline GSH remains normal because consumption is low at rest (demonstrated: normal resting GSH; PMID: 947404).
4. **Branch A (erythrocyte):** An exogenous oxidant challenge (fava bean divicine/isouramil, oxidant drugs, infection) **results in** accumulation of H₂O₂/organic peroxides that GSH-dependent peroxidases cannot clear → oxidation of hemoglobin and membrane proteins → membrane alterations → macrophage removal of damaged cells → **acute hemolytic anemia** (PMID: 8813716; PMID: 24316370).

5. **Branch B (neonatal):** The oxidative lability of neonatal red cells **results in** hemolysis-driven **neonatal jaundice/hyperbilirubinemia** (PMID: 17185460).
6. **Branch C (lens):** Chronic failure of lens GSH-dependent peroxide detoxification **leads to** lipid peroxidation and protein oxidation → **cataract** (inferred by analogy to cataractous-lens enzyme profiles; PMID: 1737065).
7. **Compensation (dampening node):** In parallel, the **thioredoxin/thioredoxin-reductase system** reduces GSSG and limits oxidative damage, **resulting in** a phenotype that is episodic rather than chronic (demonstrated in yeast and mouse; PMID: 19951944; PMID: 28686716).



Upstream vs downstream: The mutation and loss of enzyme activity are upstream; oxidant-triggered peroxide accumulation is the central node; tissue-specific damage (hemolysis, jaundice, cataract) is downstream. The Trx/TrxR system is a lateral, upstream-acting buffer that sets the overall mildness.

Cell types (CL) and anatomy (UBERON): erythrocyte (CL:0000232), neutrophil (CL:0000775), lens fiber cell (CL:0011004); blood (UBERON:0000178), lens of camera-type eye (UBERON:0000965), liver (UBERON:0002107, secondary via bilirubin handling). **Subcellular (GO CC):** cytosol (GO:0005829), mitochondrion (GO:0005739) — GR has both cytosolic and mitochondrial isoforms from the single gene.

Evidence Base

PMID	Title (abbrev.)	Evidence type	How it supports the findings
17185460	Molecular basis of GR deficiency in human blood cells	Human clinical/molecular	Defines causal LoF variants, rarity (2/>15,000), absent protein — anchors Findings 1, 2, 5, 8, 10
947404	Familial deficiency of GR in human blood cells	Human clinical	Establishes AR inheritance, favism/cataract phenotype, FAD/riboflavin non-responsiveness, normal baseline GSH — Findings 1, 2, 3, 6, 7
11924113	GR deficiency in Saudi Arabia	Human epidemiology	Quantifies acquired riboflavin-responsive form and absence of hereditary cases — Findings 3, 10
18638483	Catalytic cycle of human GR near 1 Å	Structural/in vitro	Defines the FAD/NADPH catalytic mechanism — Finding 5
22279102	GR facilitates host defense / oxidative burst / NETs	Mouse model	Neutrophil host-defense role, transient burst defect — Finding 4
28686716	GSR not essential in mouse cochlea; Trx backup	Mouse model	Thioredoxin compensation for GSR loss — Findings 4, 7, 9
8813716	Hemolytic anemias due to RBC enzyme deficiencies	Review	Mechanistic link from redox-enzyme deficiency to hemolysis — Findings 6, 10
24316370	Inborn defects in antioxidant systems of RBCs	Review	NADPH as main RBC reductant; GR deficiency context — Finding 6
1737065	Peroxide-metabolizing systems of the lens	Human/in vitro	Links reduced GR + oxidative stress to cataract — Finding 6
19769422	Perioperative management of G6PD-deficient patient	Review	Oxidant-avoidance management paradigm — Finding 7
27170501	Riboflavin status, MTHFR, blood pressure	Review	EGRAC as gold-standard functional assay — Finding 10

PMID	Title (abbrev.)	Evidence type	How it supports the findings
19951944	Trx-TrxR as alternative GSSG-reducing system in yeast	Model organism	Conserved thioredoxin backup — Finding 9
15701801	Overlapping cytoplasmic/mitochondrial redox systems in yeast	Model organism	Dual localization of GSR ortholog — Finding 9
42681644	GR deficiency potentiates ferroptosis/cuproptosis immunogenicity	In vitro/CRISPR	GSR as top ferroptosis suppressor — Finding 11
35361806	In silico analysis of deleterious GSR SNPs	Computational	Confirms disease definition; flags candidate deleterious nsSNPs
16528753	8 Mb interstitial 8p12-p21.2 deletion	Human clinical	Confirms <i>GSR</i> chromosomal location within a contiguous-gene region

Section-by-section factual summary

1. Disease information. MONDO:0019531; OMIM 618660; gene *GSR* (HGNC:4623). Synonyms: hereditary glutathione reductase deficiency, GR deficiency, GSR deficiency, hemolytic anemia due to glutathione reductase deficiency. MeSH concept: Glutathione Reductase/deficiency. Information is derived from a handful of aggregated case reports/families plus population screens — not from large EHR cohorts.

2. Etiology. Primary cause is genetic (biallelic *GSR* LoF). The sole well-established **environmental/trigger factor** is oxidative stress (fava bean ingestion — divicine/isouramil, oxidant drugs, infection). Consanguinity is a risk factor (Loos family). No protective genetic alleles are established; the thioredoxin system acts as an endogenous compensatory buffer rather than a protective "allele." **Gene–environment interaction** is the defining feature: the genotype is clinically silent until an oxidant exposure precipitates hemolysis.

3. Phenotypes. Hemolytic anemia (episodic, oxidant-triggered; HP:0001878), cataract (HP:0000518), neonatal jaundice (HP:0006579). Onset ranges from neonatal (jaundice) to childhood/adult (favism, cataract). Severity is mild-to-moderate and episodic rather than progressive. Frequencies cannot be given as robust percentages owing to the tiny number of described patients.

4. Genetic/molecular. Causal gene *GSR* (8p12). Variant types observed: large deletion (2,246 bp, LoF), nonsense (premature stop), missense (Gly330Ala, destabilizing). Functional consequence: loss of function via protein instability/loss of dimerization. gnomAD: LoF-tolerant (pLI $\approx$ 0). No established modifier genes in humans, though the Trx system is the principal functional modifier. No intrinsic epigenetic or chromosomal-abnormality mechanism, though *GSR* can be deleted within contiguous-gene 8p deletions (PMID: 16528753).

5. Environmental. Oxidant triggers (fava beans/divicine, oxidant drugs, infection). No infectious agent causes the disease.

6. Mechanism. See the causal chain and diagram above.

7. Anatomical structures. Primary: blood/erythrocytes (UBERON:0000178, CL:0000232); lens (UBERON:0000965). Secondary: liver (bilirubin handling); neutrophils (CL:0000775, host-defense — subclinical in humans). Subcellular: cytosol and mitochondria.

8. Temporal development. Onset neonatal to adult; course chronic-lifelong at the genetic level but clinically episodic/trigger-dependent; non-progressive between crises.

9. Inheritance and population. Autosomal recessive; predicted biallelic frequency $\sim$ 1 in 4 million (gnomAD); carrier frequency $\sim$ 0.1% upper bound. Complete penetrance of the biochemical deficiency; clinical expressivity variable and trigger-dependent. Consanguinity increases risk. No established sex predilection or founder population.

10. Diagnostics. Erythrocyte GR assay $\pm$ FAD; EGRAC; Western blot; *GSR* sequencing/deletion analysis; acetylphenylhydrazine glutathione-stability test. Differential: G6PD deficiency, other RBC enzymopathies.

11. Prognosis. Favorable; survival to adulthood; episodic hemolysis without chronic anemia; normal baseline GSH.

12. Treatment. Supportive only: oxidant-trigger avoidance; transfusion in crises; phototherapy/exchange transfusion for neonatal jaundice as per standard neonatology. Riboflavin ineffective for the hereditary form. **NCIT suggestions:** Blood Transfusion (NCIT:C15360), Supportive Care (NCIT:C15277), Phototherapy (NCIT:C15349).

13. Prevention. Genetic counseling for consanguineous/carrier families; trigger avoidance (tertiary prevention). No population screening is warranted given rarity.

14. Other species / natural disease. *Gsr*-null mice (NCBI Gene 14782) are viable with host-defense and lung-development phenotypes; *S. cerevisiae glr1 Δ* (YPL091W) is a standard antioxidant-deficient model. No prominent naturally occurring companion-animal disease is catalogued.

15. Model organisms. Mouse *Gsr* knockout (host defense, hyperoxic lung responses), yeast *glr1Δ* (oxidative-stress sensitivity, thioredoxin compensation). These models recapitulate the biochemical defect and the thioredoxin-buffering principle but **do not** fully reproduce the human favism-hemolysis phenotype, because mouse/yeast oxidative challenges differ from human fava-bean exposure.

Limitations and Knowledge Gaps

- **Extremely small patient base.** The entire human literature on the hereditary disease rests on a handful of families. Frequencies, penetrance, and genotype–phenotype correlations cannot be estimated with statistical confidence.
 - **Cataract causality is inferential.** The lens mechanism is supported by analogy to cataractous-lens enzyme profiles ([PMID: 1737065](#)) rather than by direct study of *GSR*-null lenses.
 - **No natural-history or registry data.** There are no longitudinal cohorts, QoL instruments, or mortality statistics specific to this disorder.
 - **gnomAD estimate is a model.** The ~1-in-4-million figure assumes LoF-variant pathogenicity; several common "LoF" alleles are 3'-terminal and likely benign, so the estimate is an upper bound on biallelic frequency and a lower bound on rarity.
 - **Human immune phenotype unquantified.** The neutrophil host-defense role is robust in mice but not demonstrated to cause clinical immunodeficiency in humans.
 - **No pharmacogenomic or targeted-therapy data** exist for the deficiency itself.
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Proposed Follow-up Experiments / Actions

1. **GeneMatcher / undiagnosed-disease network query** to assemble additional biallelic *GSR* cases and build a minimal natural-history series.
2. **Functional variant characterization:** recombinant expression and thermostability/activity assays of *GSR* missense variants (e.g., Gly330Ala) to establish an ACMG-aligned functional-evidence pipeline (PS3) for VUS classification.

3. **Patient-derived iPSC erythroid and lens-epithelial models** to directly test oxidant-challenge hemolysis and cataractogenesis, and to quantify thioredoxin-system compensation (TXN/TXNRD1 knockdown rescue experiments).
 4. **ClinVar curation:** deposit/annotate the known pathogenic alleles (2,246-bp deletion, nonsense, Gly330Ala) with supporting PMIDs to improve diagnostic interpretation.
 5. **Targeted re-analysis of hemolytic-anemia gene panels** (including *GSR*) in unexplained G6PD-normal non-spherocytic hemolytic anemia and favism-like presentations.
 6. **Therapeutic hypothesis test:** evaluate whether boosting the thioredoxin arm (or avoiding thioredoxin-reductase inhibitors such as auranofin-class drugs) modulates oxidative susceptibility in *GSR*-deficient models — a direct translation of the compensation finding.
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Consensus Answer

Glutathione Reductase Deficiency (MONDO:0019531) is an ultra-rare autosomal recessive disorder caused by biallelic loss-of-function variants in *GSR* (chromosome 8p12), the gene encoding the FAD/NADPH-dependent flavoenzyme that regenerates reduced glutathione (GSH) from GSSG; its loss cripples erythrocyte and lens antioxidant defense and produces oxidant-triggered (favism) hemolytic anemia, neonatal jaundice, and cataracts. The phenotype is usually mild and episodic because the evolutionarily conserved thioredoxin/thioredoxin-reductase system partially compensates — consistent with *GSR* being genetically loss-of-function-tolerant (gnomAD pLI $\approx$ 0; predicted biallelic frequency $\approx$ 1 in 4 million) and with viable *Gsr*-knockout mice and *glr1 Δ* yeast. This rare hereditary enzyme-null disease must be distinguished from the common acquired riboflavin-responsive deficiency (discriminated by the EGRAC), and management is limited to oxidant-trigger avoidance and supportive transfusion, since riboflavin corrects only the acquired form.
