Combined Immunodeficiency Due to GINS1 Deficiency — Comprehensive Disease Characteristics Report

Summary

Combined immunodeficiency due to GINS1 deficiency (MONDO:0044725; OMIM #617827, "Immunodeficiency 55" / IMD55) is an ultrarare, autosomal-recessive inborn error of DNA replication. It is caused by **biallelic hypomorphic (partial loss-of-function) variants in *GINS1*** (also called *PSF1*), located at chromosome 20p11.21. GINS1 encodes one of four subunits (GINS1/PSF1, GINS2/PSF2, GINS3/PSF3, GINS4/SLD5) of the **GINS complex**, an essential component of the **CDC45–MCM2-7–GINS (CMG) replicative helicase** that unwinds double-stranded DNA at the eukaryotic replication fork. Because complete loss of GINS function is embryonic-lethal, all viable human disease results from partial deficiency, with residual GINS1 activity measured at roughly **3–16%** in patient cells.

The disorder was first defined by Cottineau and colleagues in 2017, who described 5 patients from 4 kindreds and established the **core clinical triad: intrauterine (and usually postnatal) growth retardation, chronic neutropenia, and NK-cell deficiency**. Mechanistically, hypomorphic GINS1 impairs GINS complex assembly, producing basal replication stress, defective checkpoint signaling, impaired cell-cycle control, and genomic instability — all of which are rescued by wild-type GINS1. These defects selectively cripple highly proliferative cell compartments (fetal tissues driving growth; bone-marrow myeloid and NK-cell precursors), explaining the phenotype. Residual enzymatic activity correlates with the severity of growth retardation and the cellular phenotype, though the immunological phenotype is relatively uniform across genotypes.

A 2026 case report (Mackley et al.) expanded the phenotype, describing distinctive facial dysmorphism and **glaucoma** in addition to the core triad, and noted glaucoma appearing across multiple unrelated individuals — pointing toward genuine phenotypic expansion. To date only ~9–10 patients have been reported worldwide. GINS1 deficiency belongs to a small but coherent family of "**replicative-helicase NK-cell deficiencies**," most notably the closely analogous partial MCM4 deficiency (growth retardation, adrenal insufficiency, and selective

NK deficiency) and the recently described CDC45 deficiency. Management is currently supportive; no curative, disease-specific therapy has been established, although hematopoietic stem cell transplantation is the conceptual analog drawn from other combined immunodeficiencies.

Key Findings

Finding 1 — GINS1 deficiency is an autosomal-recessive combined immunodeficiency defined by a core triad

Cottineau et al. (2017, *J Clin Invest*) studied **5 patients from 4 kindreds**, all carrying compound-heterozygous rare mutations in *GINS1* (*PSF1*). Every patient displayed **intrauterine growth retardation, chronic neutropenia, and NK-cell deficiency**, and 4 of 5 also had postnatal growth retardation. This paper established both the disease entity and its defining clinical signature.

> "We studied 5 patients from 4 kindreds, all of whom displayed intrauterine growth retardation, chronic neutropenia, and NK cell deficiency. Four of the 5 patients also had postnatal growth retardation." — PMID: 28414293

The inheritance and causal chain were summarized directly:

> "Autosomal recessive, partial GINS1 deficiency impairs DNA replication and underlies intra-uterine (and postnatal) growth retardation, chronic neutropenia, and NK cell deficiency." — PMID: 28414293

A central genotype–phenotype relationship was that residual GINS1 activity graded with disease severity:

> "The residual levels of GINS1 activity reached 3% to 16% in patients' cells, depending on their GINS1 genotype, and correlated with the severity of growth retardation and the in vitro cellular phenotype." — PMID: 28414293

Gene/identifier annotations: *GINS1/PSF1*, HGNC:28980, OMIM gene *610608, chromosome 20p11.21 (Ensembl ENSG00000101003; UniProt Q14691); disease OMIM #617827 (IMD55). Evidence type:** human clinical.

Finding 2 — Mechanism: GINS1 is an essential CMG replicative-helicase subunit; deficiency causes replication stress and genomic instability

The GINS complex is a **1:1:1:1 heterotetramer** (SLD5/GINS4, PSF1/GINS1, PSF2/GINS2, PSF3/GINS3) essential for the initiation and progression of eukaryotic DNA replication. Together with CDC45 and the MCM2-7 hexamer it forms the **CMG helicase**, the molecular motor that separates the two DNA strands at the replication fork.

> "The CMG [Cdc45-Mcm2-7-GINS(Psf1-3, Sld5)] helicase unwinds the double helix to separate the leading and lagging DNA strands." — PMID: 35038632

Complete loss is incompatible with life, underscoring the essentiality of the complex:

> "The GINS complex is essential for eukaryotic DNA replication, and homozygous null mutations of GINS component-encoding genes are embryonic lethal in mice." — PMID: 28414293

Patient-derived fibroblasts provided direct cellular evidence for the pathomechanism, and crucially the defect was reversible with wild-type gene restoration:

> "The patients' fibroblasts displayed impaired GINS complex assembly, basal replication stress, impaired checkpoint signaling, defective cell cycle control, and genomic instability, which was rescued by WT GINS1." — PMID: 28414293

Evidence type: human clinical + in vitro (patient fibroblasts) + model organism (mouse lethality).

Finding 3 — Phenotypic spectrum expansion: dysmorphism, glaucoma, and variable infection burden

Mackley et al. (2026) reported a **2-year-old female** with growth retardation, chronic neutropenia, distinctive facial features, and **glaucoma**, carrying compound-heterozygous likely-pathogenic variants **c.-48C>G (p.?)** and **c.247C>T (p.Arg83Cys)**. Their review of all nine individuals reported to date reaffirmed the core triad while highlighting emerging features.

> "We present a 2-year-old female with growth retardation, chronic neutropenia, distinctive facial features, and glaucoma. Exome sequencing revealed two likely pathogenic variants in GINS1, c.-48C>G p.? and c.247C>T p.Arg83Cys." — PMID: 41689265
>
> "cementing growth retardation, neutropenia, and natural killer cell deficiency as core features." — PMID: 41689265
>
> "glaucoma has now been observed in multiple unrelated individuals, pointing toward possible phenotypic expansion." — PMID: 41689265

Notably, this proband had **no history of infections**, illustrating that the infection burden is variable and that immunodeficiency may be "mildly symptomatic" in some patients. **Evidence type:** human clinical (case report + literature review).

Finding 4 — Model organisms and related helicasopathies contextualize the disease

Multiple orthogonal models support the mechanism and place GINS1 deficiency within a disease group:

- **Mouse:** Targeted disruption of *Sld5* (GINS4) causes an inner-cell-mass proliferation defect and peri-implantation embryonic lethality, phenocopying *Psf1* (GINS1)-null mice. *Psf1* haploinsufficiency impairs acute proliferation of bone-marrow hematopoietic stem cells during 5-FU-induced regeneration.

> "targeted disruption of SLD5 in mice causes a defect in cell proliferation in the inner cell mass, resulting in embryonic lethality at the peri-implantation stage." — PMID: 24244394

> "haploinsufficiency of PSF1 resulted in failure of acute proliferation of bone marrow hematopoietic stem cells (HSCs) during reconstitution of bone marrow ablated by 5-FU treatment." — PMID: 24244394

- ***Drosophila*:** Knockdown of any of the four GINS genes (*Sld5, Psf1, Psf2, Psf3*) yields virtually identical mitotic phenotypes — chromosome condensation defects, chromosome breakage, and polyploidy — confirming the shared essential function of the complex (PMID: 40577589, PMID: 20709026).
- **Analogous human helicasopathy (MCM4):** Partial MCM4 deficiency causes a strikingly parallel human syndrome of growth retardation, adrenal insufficiency, and selective NK-cell deficiency with genomic instability — the key differential diagnosis.

> "partial MCM4 deficiency results in a genetic syndrome of growth retardation with adrenal insufficiency and selective NK deficiency." — PMID: 22354167

Together with reviews of inborn NK-cell errors (PMID: 24135998), these establish **"replicative-helicase NK deficiencies"** as a recognized category. **Evidence type:** model organism + human clinical (comparative).

Finding 5 — Genetic architecture: biallelic hypomorphic variants; heterozygotes unaffected; recurrent p.Arg83Cys

gnomAD v4 constraint metrics for *GINS1* (ENSG00000101003) show **pLI ≈ 2.5×10^{-7} (i.e., ~0)** and observed/expected LoF (oe_lof) = 0.74 (90% CI 0.55–1.03). This indicates *GINS1* is **not** loss-of-function-intolerant at the heterozygous level, fully consistent with a recessive disease in which carriers are healthy. Reported disease alleles span **5′UTR/promoter-proximal, missense, and splice classes**. The Mackley 2026 case carried:

Variant	cDNA	Protein	gnomAD exome AF	ClinVar
5′UTR	c.-48C>G	p.?	3.9×10^{-6} (5 alleles)	ultrarare
Missense	c.247C>T	p.Arg83Cys	6.6×10^{-4} (951 alleles)	conflicting classifications
Missense	c.455G>A	p.Cys152Tyr	—	Likely pathogenic

Of ~188 ClinVar *GINS1* entries, the majority are variants of uncertain significance (VUS). The preserved residual activity (3–16%) confirms these are **hypomorphic** rather than null alleles.

> "The residual levels of GINS1 activity reached 3% to 16% in patients' cells, depending on their GINS1 genotype." — PMID: 28414293
>
> "Exome sequencing revealed two likely pathogenic variants in GINS1, c.-48C>G p.? and c.247C>T p.Arg83Cys." — PMID: 41689265

Evidence type: human clinical + computational (population genetics).

Finding 6 — Disease nosology and identifiers

Resource	Identifier
MONDO	MONDO:0044725 ("combined immunodeficiency due to GINS1 deficiency")
OMIM phenotype	#617827 (Immunodeficiency 55, IMD55)
OMIM gene	*610608 (*GINS1*)
HGNC	HGNC:28980
NCBI Gene	9837
Ensembl	ENSG00000101003
UniProt	Q14691
Cytoband	20p11.21
Orphanet	"Combined immunodeficiency due to GINS1 deficiency"
MeSH	No dedicated descriptor (indexed under Severe Combined Immunodeficiency / Primary Immunodeficiency Diseases)

Synonyms: CID due to GINS1 deficiency; IMD55; combined immunodeficiency with intrauterine growth retardation–NK cell deficiency–neutropenia; PSF1 deficiency. Information is derived from **aggregated disease-level resources and individual patient case series** (not EHR-scale data).

Finding 7 — GINS1/PSF1 protein biology and structure

UniProt Q14691 (GINS1/PSF1) is a **196-amino-acid nuclear DNA-replication factor** localizing to the nucleus and chromosome. It is required for GINS complex function in the initiation and progression of DNA replication; GINS is a core component of the CMG helicase that unwinds template DNA. GINS1 forms a stable subcomplex with GINS4 (SLD5) and assembles the GINS heterotetramer (GINS1/2/3/4). Domain annotations: **Pfam PF05916 (SLD5/GINS), InterPro IPR056783**. Multiple experimental structures exist — the human GINS complex (**PDB 2E9X, 2EHO, 2Q9Q**) and cryo-EM human CMG replisome assemblies (**PDB 6XTX, 6XTY, 7PFO, 8OK2, 9E2Z**). Variant-induced failure of assembly directly links protein dysfunction to the cellular phenotype.

> "The patients' fibroblasts displayed impaired GINS complex assembly, basal replication stress, impaired checkpoint signaling, defective cell cycle control, and genomic instability." — PMID: 28414293

Finding 8 — Clinical course, diagnostics, prognosis, and management

Cottineau (2017) established that the combined neutropenia + NK-cell deficiency arises from a **maturation blockade in the bone marrow** and was "mildly symptomatic." Onset is **congenital/prenatal** (IUGR), with a chronic postnatal course; growth-retardation severity tracks residual GINS1 activity.

> "The association of neutropenia and NK cell deficiency, which is unusual among primary immunodeficiencies and bone marrow failures, was due to a blockade in the bone marrow and was mildly symptomatic." — PMID: 28414293
>
> "The residual levels of GINS1 activity reached 3% to 16% in patients' cells, depending on their GINS1 genotype, and correlated with the severity of growth retardation." — PMID: 28414293

Diagnostic workup: complete blood count (chronic neutropenia; HP:0001875); lymphocyte immunophenotyping showing reduced/absent NK cells ($CD3^{-}CD56^{+}$; NK deficiency HP:0040218) with relatively preserved T/B lymphocytes; NK cytotoxicity assays; bone-marrow examination (myeloid maturation arrest); growth assessment (IUGR/short stature HP:0001511/HP:0004322);

and cytogenetic/genomic-instability testing. **Molecular diagnosis** is via WES/WGS or targeted inborn-errors-of-immunity/bone-marrow-failure gene panels including *GINS1*, with single-gene/segregation testing confirming biallelic variants. **Evidence type:** human clinical.

Section-by-Section Report

1. Disease Information

GINS1 deficiency is an ultrarare autosomal-recessive combined immunodeficiency and inborn error of DNA replication. **Overview:** biallelic hypomorphic variants in *GINS1* partially impair the CMG replicative helicase, causing replication stress and a characteristic triad of growth retardation, chronic neutropenia, and NK-cell deficiency. **Identifiers:** MONDO:0044725; OMIM #617827 (IMD55); OMIM gene *610608; HGNC:28980; NCBI Gene 9837; Ensembl ENSG00000101003; UniProt Q14691; Orphanet "Combined immunodeficiency due to GINS1 deficiency"; no dedicated ICD-11/MeSH term (indexed under primary/severe combined immunodeficiency). Synonyms: IMD55, CID due to GINS1 deficiency, PSF1 deficiency, combined immunodeficiency with IUGR–NK deficiency–neutropenia. Source:** disease-level aggregation + individual case series (not EHR).

2. Etiology

Causal factor: monogenic — biallelic (compound heterozygous or homozygous) **hypomorphic variants in *GINS1***. **Genetic risk:** the disease requires two defective alleles; heterozygous carriers are unaffected (pLI ≈ 0). No environmental, infectious, or lifestyle cause; there are no established modifier genes, protective alleles, or gene–environment interactions. **Consanguinity** increases risk of recessive homozygosity, as with all AR disorders. Residual GINS1 activity (a genotype-dependent quantitative trait) is the principal severity determinant. PMID: 28414293

3. Phenotypes

Phenotype	Type	HPO	Onset	Frequency	Severity/ course
Intrauterine growth retardation	clinical sign	HP:0001511	prenatal	100% (5/5, 9/9)	severe, tracks residual activity
Postnatal growth retardation / short stature	clinical sign	HP:0004322	infancy	~80% (4/5)	variable
Chronic neutropenia	lab abnormality	HP:0001875	congenital	core (all)	chronic, "mildly symptomatic"
NK-cell deficiency	lab abnormality	HP:0040218	congenital	core (all)	persistent
Distinctive facial features	physical	HP:0001999	congenital	subset	emerging
Glaucoma	clinical sign	HP:0000501	early childhood	multiple unrelated	emerging
Viral susceptibility	symptom	—	variable	variable (some none)	variable

Quality-of-life impact: growth failure and chronic immune surveillance dominate; infection burden is variable and sometimes absent. PMID: 28414293, PMID: 41689265

4. Genetic/Molecular Information

Causal gene: *GINS1* (*PSF1*), 20p11.21. **Variant classes:** 5′UTR (c.-48C>G), missense (c.247C>T p.Arg83Cys; c.455G>A p.Cys152Tyr Likely pathogenic), and splice. **Population frequency:** disease alleles are rare-to-ultrarare (p.Arg83Cys AF ~6.6×10^{-4}; c.-48C>G AF ~3.9×10^{-6}). **Origin:** germline. **Functional consequence:** partial loss of function (hypomorphic) with 3–16% residual activity; not gain-of-function or dominant-negative. **Modifier genes/epigenetics/ chromosomal abnormalities:** none established. PMID: 28414293, PMID: 41689265

5. Environmental Information

No environmental, lifestyle, or infectious cause. Infections are downstream *consequences* of immunodeficiency, not triggers. Not applicable for toxin/occupational/dietary factors.

6. Mechanism / Pathophysiology

See the Mechanistic Model below. **Molecular pathway:** DNA replication initiation/elongation via the CMG helicase (GO:0006270, GO:0006260). **Cellular processes:** replication stress, S-phase/replication checkpoint signaling (GO:0000076), cell-cycle dysregulation, genomic instability. **Protein dysfunction:** impaired GINS heterotetramer assembly → destabilized CMG. **Immune involvement:** immunodeficiency via failed proliferation of NK-lineage and myeloid precursors (bone-marrow maturation blockade). **Tissue-damage mechanism:** proliferation failure/genomic instability in high-turnover compartments. PMID: 28414293, PMID: 35038632

7. Anatomical Structures Affected

Organ/system: bone marrow (UBERON:0002371) and immune system (primary); whole-body growth; eye (UBERON:0000970, glaucoma). **Cell types (CL):** natural killer cell (CL:0000623), neutrophil (CL:0000775), hematopoietic stem/progenitor cell (CL:0000037), myeloid precursors; patient fibroblasts show the cellular defect in vitro. **Subcellular (GO CC):** nucleus (GO:0005634), chromosome (GO:0005694), CMG complex (GO:0071162), GINS complex (GO:0000811). **Lateralization:** systemic/bilateral (e.g., glaucoma may be bilateral).

8. Temporal Development

Onset: congenital/prenatal (IUGR). **Course:** chronic, lifelong; growth retardation and cytopenias persist. **Progression:** generally stable rather than rapidly progressive; severity set largely at birth by residual activity. No defined staging. **Critical period:** fetal/early-childhood growth window. PMID: 28414293

9. Inheritance and Population

Inheritance: autosomal recessive. **Penetrance:** appears complete for the core triad in biallelic individuals; expressivity variable for growth severity and emerging features. **Epidemiology:** ultrarare — only ~9–10 reported patients worldwide; no formal prevalence/incidence estimate. **Carrier state:** healthy (pLI ≈ 0). **Consanguinity** relevant as for all AR disease. No confirmed founder effect, anticipation, mosaicism, or sex bias documented given the tiny cohort. PMID: 28414293, PMID: 41689265

10. Diagnostics

Laboratory: CBC (chronic neutropenia), lymphocyte immunophenotyping (reduced/absent $CD3^{-}CD56^{+}$ NK cells, preserved T/B), NK cytotoxicity assay, bone-marrow aspiration (myeloid maturation arrest), cytogenetic/genomic-instability testing (patient fibroblasts). **Genetic testing:** WES/WGS or targeted IEI/bone-marrow-failure panels including *GINS1*; single-gene/segregation confirmation of biallelic variants; functional residual-activity assay as a confirmatory research tool. **Differential diagnosis:** partial MCM4 deficiency (adds adrenal insufficiency), CDC45 deficiency, other congenital neutropenias and NK-deficiency syndromes. PMID: 28414293, PMID: 22354167

11. Outcome / Prognosis

Immunodeficiency is often **"mildly symptomatic"**; the bone-marrow blockade underlies the cytopenias. Growth-retardation severity is prognostically tied to residual GINS1 activity. Given documented genomic instability, a theoretical (unquantified) malignancy risk exists by analogy to MCM4. No survival/mortality statistics are available due to the tiny cohort. PMID: 28414293

12. Treatment

No disease-specific or curative therapy is established. Management is **supportive**: infection surveillance/prophylaxis, treatment of neutropenia-related infections, growth monitoring, and ophthalmologic care for glaucoma. Hematopoietic stem cell transplantation (NCIT:C15431) is the conceptual analog from other combined immunodeficiencies but would not correct the intrinsic non-hematopoietic growth defect; its role is undefined. No gene/cell/RNA therapy or clinical-trial data specific to GINS1.

13. Prevention

No primary prevention (monogenic, congenital). **Secondary/tertiary:** early diagnosis, infection prophylaxis, and surveillance for complications. **Genetic counseling** for recessive recurrence risk (25% in carrier couples); carrier and prenatal/preimplantation testing available once familial variants are known. No newborn-screening program targets GINS1 specifically (though NK/immune deficiencies may be flagged by TREC-based SCID screening in some cases).

14. Other Species / Natural Disease

No naturally occurring companion-animal or wildlife disease documented (OMIA has no GINS1 entry). Orthologs are highly conserved: mouse *Gins1*/*Psf1* and *Gins4*/*Sld5*; *Drosophila Psf1/Psf2/Psf3/Sld5*; yeast GINS (Sld5, Psf1-3). Evolutionary conservation of the CMG mechanism is strong across eukaryotes and archaea. Not zoonotic. PMID: 24244394, PMID: 40577589

15. Model Organisms

Mouse: *Psf1*-null and *Sld5*-null are embryonic-lethal (peri-implantation); *Psf1* haploinsufficiency impairs regenerative HSC proliferation — recapitulates the proliferation-dependence but not the viable hypomorphic human phenotype (a hypomorphic knock-in is lacking). **Drosophila:** RNAi/mutant of any GINS subunit reproduces genomic-instability/mitotic defects. **In vitro:** patient-derived fibroblasts recapitulate impaired GINS assembly, replication stress, and genomic instability, rescued by WT GINS1 — the best available disease-relevant model. **Limitation:** no model reproduces the full human triad simultaneously. PMID: 24244394, PMID: 20709026, PMID: 28414293

Mechanistic Model / Interpretation

The pathophysiology of GINS1 deficiency follows a clean causal chain from a housekeeping molecular defect to a tissue-selective clinical phenotype:

```
Biallelic hypomorphic GINS1 variants (residual activity 3–16%)
            │
            ▼
Impaired assembly of the GINS heterotetramer (GINS1/2/3/4)
            │
            ▼
Destabilized CMG helicase (CDC45–MCM2-7–GINS)
            │
            ▼
Reduced/ slowed replication-fork unwinding  →  basal REPLICATION STRESS
            │
            ▼
Impaired S-phase checkpoint signaling + defective cell-cycle control
            │
            ▼
GENOMIC INSTABILITY (chromosome breakage, ↑ single-stranded DNA)
            │
            ▼
Proliferation failure — selectively in HIGHLY DIVIDING compartments
     ├── Fetal/postnatal growth → IUGR + short stature
     ├── Bone-marrow myeloid precursors → maturation blockade → NEUTROPENIA
     └── NK-cell lineage (proliferation-dependent) → NK-CELL DEFICIENCY
            │
            ▼
Variable viral susceptibility; emerging: dysmorphism, glaucoma
```

Upstream vs downstream: The primary (upstream) lesion is a *quantitative* deficit of a structural replisome subunit. Everything downstream — replication stress, checkpoint failure, genomic instability, and cell-cycle arrest — is a generic consequence of a weakened replication machine. The **tissue selectivity** of the clinical phenotype is not explained by tissue-specific gene function (GINS1 is ubiquitous) but by **differential proliferative demand**: the cell populations that must divide fastest during fetal development and hematopoiesis are the most sensitive to a partially crippled replisome. This is the unifying principle of the "replicative-helicase disorders."

Why NK cells specifically? NK-cell development appears exquisitely proliferation-dependent, which is why selective NK deficiency is a shared signature of *GINS1*, *MCM4*, and *CDC45* defects. The mouse data reinforce this: *Psf1* haploinsufficiency specifically impairs *acute* HSC proliferation under regenerative stress, precisely the condition under which a marginal replisome is exposed.

Comparison of replicative-helicase NK deficiencies:

Feature	GINS1 deficiency	MCM4 deficiency	CDC45 deficiency
Gene / complex role	GINS subunit (CMG)	MCM2-7 helicase core (CMG)	CMG activator/component
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal dominant (allelic-expression bias)
Growth retardation	Yes (IUGR + postnatal)	Yes (short stature)	Variable
NK-cell deficiency	Yes (core)	Yes (selective, CD56dim)	Yes (variable)
Neutropenia	Yes (core)	Not prominent	Variable
Adrenal insufficiency	No	Yes (characteristic)	No
Genomic instability	Yes	Yes	Yes
Key refs	28414293	22354167 / 22354170	41867723

This comparison is diagnostically useful: the **combination of neutropenia + NK deficiency without adrenal insufficiency** favors GINS1, whereas **adrenal failure + NK deficiency** points to MCM4.

Evidence Base

PMID	Title (abbrev.)	Role in this report
28414293	*Inherited GINS1 deficiency underlies growth retardation along with neutropenia and NK cell deficiency*	**Landmark defining paper.** Establishes the disease, core triad, autosomal-recessive inheritance, hypomorphic mechanism (3–16% residual activity), and the fibroblast replication-stress phenotype. Supports Findings 1, 2, 5, 7, 8.
41689265	*Expanding Phenotype of GINS1 Deficiency: A Case Report and Review*	**Phenotype expansion.** New patient with dysmorphism and glaucoma, variant details (c.-48C>G; p.Arg83Cys), and confirmation of the core triad across 9 individuals. Supports Findings 3, 5.
35038632	*Increased contribution of DNA polymerase delta to leading-strand replication with an impaired CMG helicase*	Defines GINS role within the CMG helicase. Supports Finding 2.
24244394	*Requirement of SLD5 for early embryogenesis*	Mouse model: GINS-subunit knockout is embryonic lethal; PSF1 dosage limits HSC proliferation. Supports Finding 4.
22354167	*Partial MCM4 deficiency… growth retardation, adrenal insufficiency, and NK cell deficiency*	Analogous helicasopathy and primary differential diagnosis. Supports Finding 4.
22354170	*MCM4 mutation causes adrenal failure, short stature, and NK cell deficiency*	Corroborates MCM4 phenotype and genomic-instability/replicative-helicase theme. Context for Finding 4.
24135998	*Inborn errors of the development of human natural killer cells*	Frames NK-cell deficiencies including replicative-helicase causes. Context for Finding 4.
40577589, 20709026	*Drosophila* CMG/Sld5 studies	Show identical mitotic defects on knockdown of any GINS subunit; genomic-integrity role. Context for Finding 4.
41867723	*Autosomal dominant CDC45 deficiency…*	Related CMG-component immune disease (NK reduction). Comparative context.

PMID	Title (abbrev.)	Role in this report
31815930, 33322195, 37481989	Yeast CMG/GINS mechanism papers	Mechanistic support for replication-stress/ genomic-instability consequences of impaired GINS/CMG. Context for Finding 2.

The evidence base is internally consistent: the human genetic/clinical data (28414293, 41689265) are mechanistically explained by orthogonal model-organism and biochemical studies, and the phenotype is cross-validated by the analogous MCM4/CDC45 disorders.

Limitations and Knowledge Gaps

1. **Extremely small sample size.** The entire literature comprises ~9–10 patients from a handful of kindreds. All epidemiological, prognostic, and genotype–phenotype statements are correspondingly uncertain; no formal prevalence/incidence exists (Orphanet lists it among ultrarare immunodeficiencies without a stable point estimate).
2. **No dedicated natural-history or outcome study.** Long-term survival, malignancy risk (theoretically elevated given genomic instability, by analogy to MCM4), and adult outcomes are unknown. Life expectancy and mortality figures cannot be quantified.
3. **No disease-specific treatment evidence.** There are no clinical trials, no gene- or cell-therapy data specific to GINS1, and no FDA-approved therapy. HSCT is a conceptual analog from other CIDs but its role for GINS1 (given the *non*-hematopoietic growth phenotype it would not correct) is undefined.
4. **Variant interpretation is immature.** Most ClinVar *GINS1* entries are VUS; the recurrent p.Arg83Cys allele has conflicting classifications and a relatively high population frequency (AF ~6.6×10^{-4}), complicating pathogenicity calls. Functional assays (residual-activity measurement) are the current gold standard but are not widely available.
5. **Emerging features are provisional.** Glaucoma and facial dysmorphism are reported in a subset; their penetrance, mechanism, and true association require more cases.
6. **No direct patient-derived omics.** Transcriptomic, proteomic, metabolomic, or single-cell datasets specific to GINS1-deficient patients were not identified; mechanistic inference relies on fibroblast functional assays and model organisms.

7. **No purpose-built animal model of the human disease.** Null mice are embryonic-lethal; a hypomorphic knock-in recapitulating the human hypomorphic state has not been reported, limiting preclinical therapeutic testing.

Proposed Follow-up Experiments / Actions

1. **Build an international patient registry.** Pool the ~10 known cases and prospectively enroll new ones to define natural history, infection burden, malignancy incidence, and survival — the single highest-value action for this ultrarare disease.
2. **Generate a hypomorphic GINS1 mouse (or zebrafish) knock-in** reproducing 3–16% residual activity, to model the *viable* human phenotype (growth retardation, neutropenia, NK deficiency) and serve as a preclinical platform. Null models are uninformative because they are lethal.
3. **Functional variant-classification pipeline.** Develop a standardized cellular assay (GINS complex assembly + residual replication activity + genomic-instability readout) to reclassify the many *GINS1* VUS, especially p.Arg83Cys, and correlate residual activity with clinical severity across more genotypes.
4. **Single-cell profiling of patient bone marrow and NK-lineage cells** to pinpoint the exact developmental stage of the maturation blockade and test the "proliferation-demand" hypothesis for lineage selectivity.
5. **Systematic screening for glaucoma and dysmorphism** in all diagnosed patients to establish penetrance and determine whether ophthalmologic surveillance should be standard of care.
6. **Assess long-term cancer risk** given documented genomic instability, with structured surveillance protocols mirroring those used in MCM4 deficiency and other chromosomal-instability syndromes.
7. **Evaluate whether HSCT corrects the hematologic/immune phenotype** (neutropenia, NK deficiency) while recognizing it cannot address the intrinsic growth defect — clarify the risk/benefit in symptomatic patients.

Consolidated Ontology Term Suggestions

- **Disease:** MONDO:0044725
- **Gene/protein:** HGNC:28980 (*GINS1*); UniProt Q14691
- **Phenotypes (HPO):** Intrauterine growth retardation HP:0001511; Short stature HP:0004322; Neutropenia HP:0001875; NK-cell deficiency HP:0040218; Glaucoma HP:0000501; Abnormal facial shape HP:0001999
- **Biological processes (GO):** DNA replication GO:0006260; DNA replication initiation GO:0006270; DNA unwinding involved in DNA replication GO:0006268; cell-cycle checkpoint signaling GO:0000075; DNA replication checkpoint GO:0000076
- **Cellular components (GO):** CMG complex GO:0071162; GINS complex GO:0000811; nucleus GO:0005634; chromosome GO:0005694
- **Cell types (CL):** natural killer cell CL:0000623; neutrophil CL:0000775; hematopoietic stem cell CL:0000037
- **Anatomy (UBERON):** bone marrow UBERON:0002371; eye UBERON:0000970
- **Treatment (NCIT):** Hematopoietic stem cell transplantation NCIT:C15431 (conceptual analog); supportive care NCIT:C15277

Report compiled from 5 iterations of autonomous investigation, 8 confirmed findings, and 27 reviewed papers. Primary evidence: Cottineau et al. 2017 (PMID: 28414293) and Mackley et al. 2026 (PMID: 41689265).
