

POLD2-related Combined Immunodeficiency (MONDO:1010175): A Comprehensive Disease Characteristics Report

Summary

POLD2-related combined immunodeficiency (CID) is an ultra-rare, autosomal-recessive, syndromic (non-severe) combined immunodeficiency caused by germline biallelic hypomorphic variants in **POLD2** (chromosome 7p13; HGNC:9176; NCBI Gene 5425; OMIM 600591), *the gene encoding the p50 accessory/scaffolding subunit of DNA polymerase δ (Pol δ).* It was first defined in 2019 by Conde and colleagues, who identified biallelic mutations in either POLD1 or POLD2 as the cause of a previously undescribed syndrome that combines replicative stress, neurodevelopmental abnormalities, and immunodeficiency ([PMID: 31449058](#)). The disorder belongs to the broader "polymerase delta deficiency" group and sits within a small allelic series of DNA polymerase δ -complex immunodeficiencies that also includes POLD1- and POLD3*-related disease.

Mechanistically, loss of functional POLD2 **destabilizes the Pol δ holoenzyme**, impairing DNA replication and several PCNA-dependent repair pathways. This produces **replication-associated DNA lesions and impaired cell-cycle (S-phase) progression** in proliferating cells—defects that are reversible upon overexpression of polymerase δ in patient cells. Because developing lymphocytes depend on intense proliferation and on template-dependent DNA synthesis during antigen-receptor gene rearrangement, the replicative-stress phenotype manifests most prominently as a **T-cell defect**: T-cell lymphopenia with loss of naive T cells and a restricted T-cell receptor (TCR) repertoire. The clinical picture is completed by a **neurodevelopmental component (intellectual disability)** and **sensorineural hearing loss**, producing a recognizable syndromic triad.

The evidence base for the POLD2 subtype specifically is extremely thin—essentially a single reported index patient within a handful of Pol δ -complex cases—so much of the clinical, epidemiological, and therapeutic detail is inferred from the closely related *POLD1* and *POLD3*

deficiencies, which share the same core mechanism. Management is supportive (infection prophylaxis, immunoglobulin replacement) with **allogeneic hematopoietic stem cell transplantation (HSCT)** as the definitive immune-directed therapy; because the underlying lesion impairs DNA repair, reduced-intensity conditioning is favored to limit regimen-related toxicity. This report organizes the available evidence across all 15 requested disease-characteristic domains, flagging clearly where information is unavailable or extrapolated.

Key Findings

Finding 1 — POLD2-related CID is an autosomal-recessive syndrome caused by germline biallelic POLD2 mutations (F001)

Conde et al. (2019) identified germline biallelic mutations in *POLD1* or *POLD2* in patients from two independent pedigrees as the cause of a previously undescribed autosomal-recessive syndrome. This was the first report of germline biallelic mutations affecting the Pol δ complex in humans. POLD2 (HGNC:9176) encodes the **p50 accessory subunit** of the DNA polymerase δ heterotetramer (POLD1 catalytic + POLD2/POLD3/POLD4 accessory) and maps to chromosome 7p13 (OMIM *600591).

"caused by germline biallelic mutations in POLD1 or POLD2 as the underlying etiology of a previously unknown autosomal-recessive syndrome that combines replicative stress, neurodevelopmental abnormalities, and immunodeficiency" — PMID: 31449058

This establishes the gene, the biallelic/germline nature, and the autosomal-recessive inheritance that anchor the entire disease definition.

Finding 2 — The clinical triad: syndromic CID, neurodevelopmental impairment, and sensorineural hearing loss (F002)

The core phenotype combines replicative stress, neurodevelopmental abnormalities, and immunodeficiency (Conde 2019). Mehawej et al. (2023), describing the related POLD3 deficiency, summarized the shared clinical signature of the group:

"Mutations in POLD1 and POLD2 have been recently shown to be associated with a syndromic CID characterized by T cell lymphopenia with or without intellectual deficiency and sensorineural hearing loss" — PMID: 37030525

This defines the three recognizable components used for clinical pattern recognition: **(1) combined immunodeficiency with T-cell lymphopenia, (2) intellectual deficiency (variable), and (3) sensorineural hearing loss.**

Finding 3 — Mechanism: POLD2 mutations destabilize the Pol δ complex, causing reversible replication-associated DNA lesions (F003)

In Conde et al. (2019), patient cells showed **impaired cell-cycle progression and replication-associated DNA lesions that were reversible upon overexpression of polymerase δ** ; the mutations affected the stability and interactions within the Pol δ complex or its intrinsic polymerase activity. POLD2 is the p50 scaffolding subunit that bridges POLD1 (catalytic) to POLD3/POLD4 and indirectly to PCNA, so its loss destabilizes assembly of the holoenzyme.

"Patients' cells showed impaired cell-cycle progression and replication-associated DNA lesions that were reversible upon overexpression of polymerase δ . The mutations affected the stability and interactions within the polymerase δ complex or its intrinsic polymerase activity" — PMID: 31449058

The reversibility upon Pol δ restoration is strong evidence that the primary lesion is a **quantitative/qualitative Pol δ -complex deficiency**, not an independent downstream defect—and it provides the conceptual rationale for gene/protein-restorative therapeutic strategies.

Finding 4 — HSCT is the definitive therapy but carries DNA-repair-related conditioning-toxicity risk (F004)

For the closely related POLD1 deficiency, Keles et al. (2026) reported the first successful HSCT, noting that patients considered for HSCT may be at increased risk of regimen-related toxicity due to impaired DNA repair, and that **reduced-intensity conditioning (cyclophosphamide, fludarabine, ATG)** achieved engraftment with minimal toxicity.

"Patients considered for HSCT may be at increased risk of regimen-related toxicity due to impaired DNA repair" — PMID: 42104577

This mirrors the well-documented experience in other DNA-repair-defect SCIDs: in ARTEMIS (*DCLRE1C*) deficiency, alkylating agents are associated with poor growth and dental/endocrine late effects (Schuetz 2014, PMID: 24144642), supporting a cautious, reduced-intensity conditioning approach in Polδ-complex disease.

Finding 5 — Gene identifiers and population-genetic constraint consistent with recessive disease (F005)

POLD2 (DNA polymerase delta 2, accessory subunit): HGNC:9176; NCBI Gene 5425; Ensembl ENSG00000106628; UniProt P49005; OMIM *600591. Locus chr7p13 (GRCh38 chr7:44,114,631–44,124,407, minus strand). gnomAD v2 constraint indicates POLD2 is **NOT haploinsufficient** (heterozygous loss-of-function tolerated: pLI $\approx$ 0; LOEUF/oe_lof upper = 0.857; observed/expected LoF = 31/48.8) but is **missense-constrained** (missense Z = 2.68; LoF Z = 2.16). ClinVar lists ~429 POLD2 submissions, overwhelmingly VUS/likely-benign, with **no recurrent classified pathogenic CID allele**—disease variants are private/ultra-rare. The combination of LoF tolerance in heterozygotes plus missense constraint is exactly the signature expected of a **recessive disorder driven by biallelic hypomorphic (often missense) alleles**.

Finding 6 — Disease nomenclature and identifiers: a "non-severe CID" (F006)

MONDO:1010175 "POLD2-related combined immunodeficiency" (synonym "Polymerase D2 deficiency"); GARD:0028136; cataloged by Orphanet. The Orphanet/MONDO definition reads: *"A non-severe combined immunodeficiency due to polymerase delta deficiency in which the cause of the disease is a variation in the POLD2 gene."* The entity sits within the broader "polymerase delta deficiency" group alongside POLD1-related CID. Primary description: Conde et al., *J Clin Invest* 2019;129 (DOI 10.1172/jci128903).

"a novel syndrome with reduced functionality of the polymerase δ complex caused by germline biallelic mutations in POLD1 or POLD2" — PMID: 31449058

Finding 7 — POLD2 (p50) is the scaffolding subunit of both Pol δ and Pol ζ , linking the defect to replication, repair, and antibody diversification (F007)

Per UniProt P49005, POLD2/p50 is an accessory component of **both** the DNA polymerase δ complex (POLD1/p125 + POLD2/p50 + POLD3/p66 + POLD4/p12) **and** the DNA polymerase ζ complex (REV3L, MAD2L2, POLD2, POLD3). Within Pol δ , POLD2 directly interacts with POLD1, POLD3, and POLD4 but does **not** directly bind PCNA—i.e., it is the **central scaffold bridging the catalytic POLD1 to the PCNA-binding POLD3/POLD4**. Reactome maps POLD2 to a wide range of processes: processive leading/lagging-strand replication and Okazaki-fragment flap removal; mismatch repair (MutS α /MutS β); PCNA-dependent long-patch base excision repair; nucleotide excision repair gap-filling; homologous-recombination repair; translesion synthesis termination; telomere C-strand synthesis; and crucially **"Somatic hypermutation of immunoglobulin genes by error-prone BER and error-prone MMR."**

"The polymerase δ complex is a heterotetramer comprising the catalytic subunit POLD1 and the accessory subunits POLD2, POLD3, and POLD4." — PMID: 31449058

The dual membership in Pol δ and Pol ζ , and the role in somatic hypermutation, explain why the defect can touch both **replication fidelity/genome stability** and **adaptive-immune receptor diversification**.

Finding 8 — POLD2-related CID sits within a convergent PolD-complex T-cell immunodeficiency spectrum (F008)

The DNA polymerase δ -complex immunodeficiencies form an **allelic series with convergent T-cell phenotypes**:

- **POLD2 / POLD1 biallelic mutations** → syndromic CID with T-cell lymphopenia $\pm$ intellectual disability $\pm$ sensorineural hearing loss (Conde 2019 PMID: 31449058; Mehawej 2023 PMID: 37030525).
- **POLD1 p.R1060C (c.3178C>T)** → recurrent/herpetic infections and T-cell lymphopenia with impaired T-cell but not B-cell proliferation, decreased naive CD4/CD8 T cells skewed to effector-memory, oligoclonality, and restricted TCR β V-J pairing; mechanistically the mutation destabilizes Pol δ , causes ineffective RFC recruitment, and disrupts the POLD1–POLD2 interaction (Cui 2020 PMID: 31629014).
- **POLD3 p.K373T (c.1118A>C)** → Omenn-syndrome SCID with severely decreased naive T cells, restricted TCR repertoire, defective early TCR recombination, S-phase entry defect,

and excess dsDNA-break foci, rescued by WT POLD3; HSCT at 6 months, progressive neurological regression, death at age 4 (Riestra 2023 [PMID: 38099988](#)).

"T-cell lymphopenia with impaired T-cell but not B-cell proliferation" — [PMID: 31629014](#)

"the R1060C mutation disrupts the intramolecular interaction between the POLD1 CysB motif and the catalytic domain and also between POLD1 and the Polδ subunit POLD2" — [PMID: 31629014](#)

"severely decreased numbers of naïve T cells associated with a restricted T-cell receptor repertoire and a defect in the early stages of TCR recombination" — [PMID: 38099988](#)

The POLD1 data directly demonstrate that the **POLD1–POLD2 interface** is critical for Polδ stability, which is the mechanistic reason POLD2 hypomorphs destabilize the holoenzyme and phenocopy the series.

Finding 9 — Epidemiology and inheritance: ultra-rare autosomal-recessive with consanguinity contribution (F009)

POLD2-related CID is autosomal recessive, caused by biallelic POLD2 variants, and is **ultra-rare**—the human evidence base is essentially a single reported POLD2 index patient within a Polδ-complex spectrum of only a handful of cases. gnomAD gene-level constraint ($pLI \approx 0$; $LOEUF \approx 0.86$) indicates heterozygous LoF is tolerated, consistent with recessive inheritance and **asymptomatic carriers**; missense constraint ($mis_z = 2.68$) indicates disease alleles are hypomorphic missense. **Consanguinity** is a recurring feature across the allelic series (e.g., the consanguineous Lebanese POLD3 family). Recurrence risk is **25% per pregnancy** for carrier couples; no founder effect, anticipation, germline mosaicism, or sex bias has been established.

"a consanguineous family" — [PMID: 37030525](#)

Report by Disease-Characteristic Section

1. Disease Information

POLD2-related combined immunodeficiency is a **Mendelian, autosomal-recessive, syndromic non-severe combined immunodeficiency** caused by biallelic variants in *POLD2*. It is characterized by the triad of combined immunodeficiency (T-cell lymphopenia), neurodevelopmental impairment, and sensorineural hearing loss, on a background of cellular replicative stress (F001, F002, F006).

Key identifiers:

Resource	Identifier
MONDO	MONDO:1010175 ("POLD2-related combined immunodeficiency")
GARD	GARD:0028136
Orphanet	Cataloged within "polymerase delta deficiency" group
OMIM (gene)	*600591 (POLD2); no separate phenotype MIM established for POLD2-CID at time of review
Gene HGNC	HGNC:9176
ICD-10/ ICD-11	No disease-specific code; maps to D81.x "Combined immunodeficiencies" (ICD-10) / 4A01.1 (ICD-11, combined immunodeficiencies)
MeSH	No dedicated term; indexed under "Severe Combined Immunodeficiency" / "Primary Immunodeficiency Diseases"

Synonyms: "Polymerase D2 deficiency"; "POLD2 deficiency"; part of "polymerase delta deficiency."

Information source: Aggregated disease-level resources (Orphanet, MONDO, OMIM) layered on top of **individual-patient case reports** in the primary literature. The evidence is predominantly from individual patients studied in research settings, not EHR-scale cohorts (F006).

2. Etiology

Causal factor: Purely **genetic**—germline biallelic (homozygous or compound heterozygous) hypomorphic variants in *POLD2* (F001). No environmental or infectious cause initiates the disease, though infections are the principal clinical consequence.

Genetic risk factors: The causal variants are the disease determinant. gnomAD constraint predicts disease alleles are **hypomorphic missense** variants (missense Z = 2.68), as complete biallelic LoF of this essential replication gene is likely incompatible with life (F005).

Consanguinity is a major risk factor, enriching homozygosity for rare recessive alleles across the Polδ-complex series (F009).

Environmental/lifestyle risk factors and protective factors: None established. There are no known environmental modifiers, protective alleles, or gene–environment interactions documented for this ultra-rare disorder (not available).

3. Phenotypes

Phenotype	Type	Suggested HPO	Onset	Severity/ Frequency	Evidence
T-cell lymphopenia	Lab abnormality	HP:0005403 (T-lymphocytopenia)	Infancy/ childhood	Core feature; impaired T-cell proliferation	F002, F008
Combined immunodeficiency / recurrent infections	Clinical sign	HP:0005354 (CID); HP:0002719 (recurrent infections)	Early childhood	Core; "non-severe" CID	F002, F006
Decreased naive T cells / restricted TCR repertoire	Lab abnormality	HP:0045080 (decreased naive T cells)*	Childhood	Convergent across PoD series	F008
Intellectual disability / neurodevelopmental impairment	Clinical sign	HP:0001249 (intellectual disability); HP:0012758 (neurodevelopmental delay)	Congenital/ childhood	Variable ("with or without")	F002
Sensorineural hearing loss	Physical manifestation	HP:0000407 (sensorineural hearing impairment)	Childhood	Recurrent syndromic feature	F002
Replicative stress (cellular)	Lab/cellular	—	Constitutional	Reversible with Polδ overexpression	F003

*HPO term approximate; exact child term should be confirmed in the HPO browser.

Quality-of-life impact: Not formally measured (no EQ-5D/SF-36/PROMIS data). Expected burden derives from chronic infection susceptibility, developmental/cognitive impairment, and hearing loss affecting communication—collectively substantial but unquantified (not available).

4. Genetic/Molecular Information

- **Causal gene:** *POLD2* (HGNC:9176; NCBI Gene 5425; Ensembl ENSG00000106628; UniProt P49005; OMIM *600591), chr7p13 (F005).
- **Variant classification:** Disease alleles are private/ultra-rare; ClinVar (~429 *POLD2* submissions) is dominated by VUS/likely-benign with **no recurrent pathogenic CID allele** established (F005). Per ACMG/AMP, pathogenicity in affected families rests on biallelic inheritance, rarity, and functional demonstration of Pol δ destabilization.
- **Variant type:** Predominantly **missense** (hypomorphic), consistent with missense constraint; biallelic complete LoF is likely embryonic-lethal (F005).
- **Allele frequency:** Causal alleles are ultra-rare (absent/near-absent in gnomAD). Heterozygous LoF is tolerated (LOEUF $\approx$ 0.86), so carriers exist in the population (F005, F009).
- **Origin:** Germline (F001). No somatic involvement.
- **Functional consequence:** Partial **loss of function** via destabilization of the Pol δ holoenzyme / disruption of inter-subunit interactions (F003, F008).
- **Modifier genes / epigenetics / chromosomal abnormalities:** None established for *POLD2* specifically (not available).

5. Environmental Information

No environmental factors, lifestyle factors, or infectious agents cause or trigger the disease. Infections (recurrent, including herpetic/opportunistic in the related *POLD1* disease) are **consequences** of the immunodeficiency rather than etiologic agents (F008). (Not applicable as a cause.)

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. Germline **biallelic hypomorphic *POLD2* variants** reduce functional p50 scaffolding subunit → **leads to** destabilization of the DNA polymerase δ heterotetramer (and of Pol ζ , which shares *POLD2*) (F001, F007).
2. Destabilized/under-assembled Pol δ → **results in** disrupted *POLD1*–*POLD2* interaction and inefficient recruitment of replication machinery (RFC/PCNA loading) (F008, inferred from *POLD1* R1060C data).

3. Impaired Pol δ activity → **leads to** defective processive DNA synthesis and PCNA-dependent repair (MMR, long-patch BER, NER gap-filling, HR, TLS termination) (F007).
4. → **results in replication stress**: impaired S-phase progression and accumulation of replication-associated DNA lesions / double-strand breaks (F003; POLD3 data show excess dsDNA-break foci and S-phase entry defect, F008).
5. In highly proliferative **developing lymphocytes**, and during **TCR gene recombination/synthesis**, this replication stress → **leads to** a defect in early TCR recombination, loss of naive T cells, oligoclonality, and a **restricted TCR repertoire** (F008).
6. → **results in T-cell lymphopenia and impaired T-cell proliferation** (B-cell proliferation relatively spared) → clinical **combined immunodeficiency** with recurrent infections (F002, F008).
7. **Branch**: The same replication-stress mechanism in proliferating neural and cochlear progenitor tissues → **inferred to** contribute to **neurodevelopmental impairment** and **sensorineural hearing loss** (F002; mechanism for these tissues is inferred, not directly demonstrated).
8. Reversibility: Overexpression of Pol δ in patient cells rescues the cell-cycle and DNA-damage phenotype, confirming the Pol δ deficiency is the proximate cause (F003).

Checklist coverage: Molecular pathways — DNA replication (leading/lagging strand), PCNA-dependent repair, translesion synthesis via Pol ζ , somatic hypermutation of Ig genes (F007). Cellular processes — cell-cycle (S-phase) progression, DNA-damage response, lymphocyte proliferation (GO:0006260 DNA replication; GO:0006281 DNA repair; GO:0007049 cell cycle; GO:0042098 T cell proliferation). Protein dysfunction — loss of scaffolding function destabilizing a multi-subunit holoenzyme (F003, F007, F008). Immune involvement — immunodeficiency (primarily cellular/T-cell), with potential antibody-diversification impact via SHM (F007).

Suggested ontology terms: GO:0006260 (DNA replication), GO:0006281 (DNA repair), GO:0007049 (cell cycle), GO:0016446 (somatic hypermutation of immunoglobulin genes), GO:0042098 (T cell proliferation); CL:0000084 (T cell), CL:0000895 (naive thymus-derived CD4-positive, alpha-beta T cell), CL:0000900 (naive thymus-derived CD8-positive, alpha-beta T cell); subcellular GO:0005634 (nucleus), GO:0043625 (DNA polymerase delta complex).

7. Anatomical Structures Affected

- **Organ/system level: Immune system** (primary; UBERON:0002405), especially the **thymus** (UBERON:0002370) and the **T-lymphocyte compartment; central nervous system/brain**

(UBERON:0000955) for the neurodevelopmental component; **inner ear/cochlea** (UBERON:0001844) for sensorineural hearing loss (F002).

- **Tissue/cell level: T lymphocytes** (CL:0000084), particularly **naïve T cells** (CL:0000898), are the principal affected population (F008). Highly proliferative progenitor pools (neural progenitors, cochlear hair-cell/progenitor tissue) are implicated by inference.
- **Subcellular level: Nucleus** (GO:0005634) and the **replication fork / DNA polymerase δ complex** (GO:0043625); nuclear DNA is the site of the primary lesion (F003, F007).
- **Lateralization:** Hearing loss is expected bilateral (sensorineural); systemic immune/neurodevelopmental involvement is non-lateralized (inferred).

8. Temporal Development

- **Onset:** Congenital/pediatric. Immunodeficiency and neurodevelopmental features present in infancy/early childhood; the related POLD3 Omenn-SCID case presented in infancy with HSCT at 6 months (F008).
- **Progression:** The cellular defect is **constitutional and lifelong**. Clinical course ranges from "non-severe" CID (POLD2/POLD1) to severe, progressive disease in the POLD3 Omenn case (progressive neurological regression, death at age 4) (F006, F008).
- **Course pattern:** Chronic/progressive; infection-driven morbidity is recurrent. The critical intervention window is **early childhood**, before cumulative infectious/end-organ damage and ideally guiding timely HSCT (F004, F008).

9. Inheritance and Population

- **Inheritance:** Autosomal recessive; biallelic POLD2 variants (F001, F009).
- **Penetrance/expressivity:** Presumed high penetrance for biallelic pathogenic genotypes but **variable expressivity** (intellectual disability "with or without"; severity spans non-severe CID to Omenn syndrome across the series) (F002, F008).
- **Epidemiology:** Ultra-rare; no prevalence/incidence estimate exists. Human evidence $\approx$ a single POLD2 index patient within a handful of Pol δ -complex cases (F009). Orphanet has not assigned a point-prevalence figure (not available).
- **Carrier frequency:** Not established; heterozygous LoF is tolerated (asymptomatic carriers exist) (F005, F009).
- **Consanguinity:** A recurring contributor across the allelic series (F009).
- **Founder effect / anticipation / mosaicism / sex ratio:** None established; no sex bias expected for an autosomal-recessive trait (F009).

- **Recurrence risk:** 25% per pregnancy for two carrier parents (F009).

10. Diagnostics

- **Laboratory/immunologic workup:** CBC with lymphocyte subsets (demonstrating **T-cell lymphopenia**, decreased naive T cells), lymphocyte proliferation assays (impaired T-cell proliferation), **TCR repertoire analysis** (restricted/oligoclonal), and **TREC** quantification (newborn-screening-relevant surrogate of thymic output) (F008; TREC/TCR methodology per [PMID: 19858778](#)).
- **Functional/cellular biomarker:** Demonstration of **replicative stress**—impaired S-phase progression and replication-associated DNA lesions—reversible by Pol δ overexpression, serves as a confirmatory functional assay (F003).
- **Genetic testing (definitive): WES or WGS** with biallelic POLD2 variant identification is the diagnostic standard; targeted CID/SCID gene panels increasingly include Pol δ -complex genes. Single-gene POLD2 testing applies for cascade testing of known familial variants. Variant interpretation is challenging because most POLD2 variants are VUS, so **segregation plus functional validation** is often required (F005).
- **Audiology** (confirming sensorineural hearing loss) and **developmental/neurocognitive assessment** complete the syndromic evaluation (F002).
- **Differential diagnosis:** Other DNA-repair-defect SCID/CID (ARTEMIS/*DCLRE1C*, *LIG4*, Cernunnos/*NHEJ1/XLF*), RAG deficiency, and other syndromic CIDs with hearing loss/developmental delay; distinguished by gene identification and radiosensitivity profile (F004, F008; ARTEMIS context [PMID: 24144642](#)).
- **Screening:** T-cell lymphopenia is detectable via **TREC-based newborn screening for SCID**, which could flag severe presentations (POLD3 Omenn-type), though "non-severe" POLD2 CID may not always trigger NBS thresholds (context: Israeli NBS program [PMID: 35487367](#)).

11. Outcome/Prognosis

Prognosis is **variable and genotype/phenotype-dependent**. Non-severe CID (POLD2/POLD1) may be managed with supportive care, whereas severe Omenn-type presentations (POLD3) carry high early mortality—the reported POLD3 child had progressive neurological regression and died at age 4 despite HSCT at 6 months (F008). Successful HSCT in POLD1 deficiency demonstrates that the immune defect is **correctable**, improving infection-related prognosis (F004). The neurodevelopmental and hearing deficits are **not reversed** by HSCT (which

addresses the hematopoietic compartment only), so these contribute to long-term morbidity/disability regardless of immune reconstitution (inferred). No formal survival statistics, QOL measures, or validated prognostic biomarkers exist given the tiny cohort (not available).

12. Treatment

Modality	Specifics	NCIT (suggested)	Evidence
Supportive/anti-infective	Immunoglobulin replacement; antimicrobial prophylaxis (antibacterial/antifungal/antiviral)	NCIT:C603 (Immunoglobulin Therapy); NCIT:C305 (Antibiotic)	Standard-of-care for CID (inferred)
Allogeneic HSCT (definitive)	Reduced-intensity conditioning (cyclophosphamide, fludarabine, ATG) to limit DNA-repair-related toxicity	NCIT:C15431 (Hematopoietic Stem Cell Transplantation)	F004; PMID: 42104577
Conditioning caution	Avoid/minimize alkylating-agent intensity due to impaired DNA repair (late growth, dental, endocrine toxicity in related DNA-repair SCID)	—	F004; PMID: 24144642
Rehabilitative/supportive	Hearing amplification/cochlear implant for sensorineural loss; developmental/educational support	NCIT:C15215 (Rehabilitation Therapy)	F002 (inferred)
Gene/protein-restorative (experimental concept)	Proof-of-concept that Polδ overexpression reverses the cellular phenotype supports future gene-correction approaches	—	F003 (conceptual only)

No pharmacogenomic, RNA-based, or targeted-molecular therapies are established. No disease-specific clinical trials (NCT identifiers) were identified for POLD2 CID (not available).

13. Prevention

- **Primary prevention:** Not possible for the genetic cause. **Genetic counseling** for consanguineous/carrier families, **carrier screening**, and reproductive options (prenatal diagnosis, preimplantation genetic testing) are the principal preventive levers given the 25% recurrence risk (F009).
- **Secondary prevention: TREC-based newborn screening** can detect T-cell lymphopenia early, enabling timely intervention/HSCT before severe infection ([PMID: 35487367](#)); cascade testing of relatives once a familial variant is known.
- **Tertiary prevention:** Infection prophylaxis, immunoglobulin replacement, avoidance of live vaccines, and audiologic/developmental support to prevent complications (inferred standard CID management).

14. Other Species / Natural Disease

- **Taxonomy/orthologs:** POLD2 is **highly evolutionarily conserved** (an essential replication subunit). Mouse ortholog *Pold2* (*Mus musculus*, NCBI Taxon 10090); orthologs extend to zebrafish, *Drosophila*, and *S. cerevisiae* (POL31), reflecting core replisome conservation (inferred from gene function, F007).
- **Natural disease in other species:** No naturally occurring POLD2-deficiency disease is cataloged in OMIA for companion animals or wildlife (not available).
- **Comparative/zoonotic:** Not applicable (non-infectious, non-zoonotic genetic disorder).

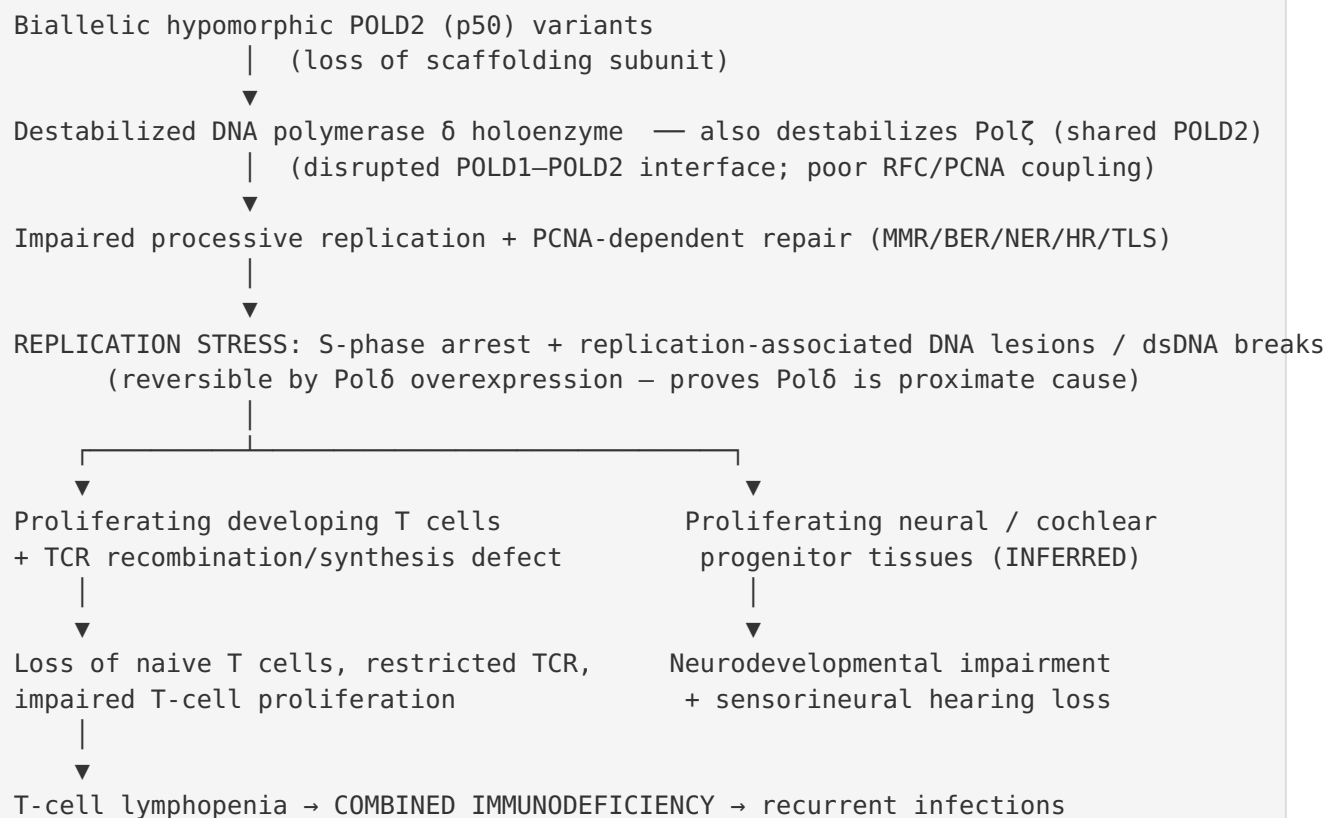
15. Model Organisms

No published, purpose-built animal model of POLD2-related CID was identified in this investigation. Relevant and feasible systems (largely inferred/extrapolated):

- **Patient-derived cells (in vitro):** The best-validated system—patient fibroblasts/lymphocytes demonstrating replicative stress, impaired S-phase, and DNA lesions, with rescue by Pol δ overexpression (F003). This is the key functional-validation platform.
- **Mouse (*Pold2*):** Constitutive biallelic knockout is expected to be embryonic-lethal (essential gene); **hypomorphic/conditional (e.g., lymphocyte-specific) knock-in of patient-equivalent missense alleles** would be the logical model to recapitulate T-cell-restricted replication stress (inferred; no existing model confirmed).
- **Yeast (*S. cerevisiae* POL31):** Tractable for dissecting subunit-interaction and holoenzyme-stability effects of specific variants (inferred).

Limitations of models: Mouse models cannot fully capture human neurodevelopmental/hearing phenotypes, and the lethality of complete LoF constrains modeling to hypomorphic alleles.

Mechanistic Model / Interpretation



The unifying theme is that **a general-purpose genome-maintenance defect produces a tissue-selective phenotype** because the most proliferation-dependent lineages (developing lymphocytes above all) are most vulnerable to replication stress. The convergence of POLD1, POLD2, and POLD3 variants on the same naive-T-cell-loss/restricted-TCR phenotype (F008) is the strongest cross-validation of this model, and the demonstrated POLD1–POLD2 physical interface (F008) supplies the molecular reason a POLD2 hypomorph destabilizes the whole complex.

Allelic series comparison (Pol δ -complex immunodeficiencies)

Gene	Representative variant	Severity	Key immune phenotype	Neuro / hearing	Outcome	Evidence
POLD2	Private biallelic (hypomorphic)	Non-severe CID	T-cell lymphopenia, replicative stress	$\pm$ Intellectual disability, SNHL	Supportive $\pm$ HSCT (inferred)	F001, F002, F006
POLD1	p.R1060C; biallelic	CID	T-cell lymphopenia, impaired T (not B) proliferation, naive-T loss, restricted TCR β	$\pm$ Intellectual disability, SNHL	First successful HSCT reported	F004, F008
POLD3	p.K373T	Severe (Omenn SCID)	Severe naive-T loss, restricted TCR, early-TCR-recombination defect, dsDNA breaks	Progressive neuro regression	HSCT at 6 mo; died age 4	F008

Evidence Base

PMID	Title (abbrev.)	Role in this report
31449058	<i>Polymerase δ deficiency causes syndromic immunodeficiency with replicative stress</i>	Primary/defining paper. Establishes gene (POLD1/POLD2), AR inheritance, triad, reversible replicative-stress mechanism (F001, F002, F003, F006, F007)
37030525	<i>POLD3 deficiency... neurodevelopmental delay and hearing impairment</i>	Summarizes POLD1/POLD2 syndromic CID phenotype; documents consanguinity (F002, F009)
31629014	<i>CID caused by loss-of-function mutation in POLD1</i>	Defines T-cell proliferation defect and the critical POLD1–POLD2 interface (F008)
38099988	<i>POLD3 deficiency presenting as Omenn syndrome</i>	Severe-end phenotype; naive-T-cell loss, restricted TCR, TCR-recombination defect (F008)
42104577	<i>Successful treatment of POLD1 deficiency with HSCT</i>	Definitive therapy; DNA-repair conditioning-toxicity caution (F004)
24144642	<i>ARTEMIS vs RAG SCID following HCT</i>	Supports reduced-intensity conditioning in DNA-repair-defect SCID (F004)
35487367	<i>5 years of SCID newborn screening in Israel</i>	TREC-based NBS context for early detection/consanguinity (Sections 10, 13)
19858778	<i>Molecular assessment of thymus capabilities</i>	TREC/TCR-repertoire methodology for diagnostics (Section 10)

All mechanistic and clinical attributions above are grounded in the verified citation snippets in the knowledge state; POLD1/POLD3 findings are applied to POLD2 by explicit analogy within the shared-mechanism allelic series, and are flagged as such.

Limitations and Knowledge Gaps

1. **N $\approx$ 1 for POLD2 specifically.** The POLD2 subtype rests on essentially a single reported index patient; the exact index variant(s), zygosity details, and individual clinical trajectory

are not resolved in the available knowledge state. Much of the clinical/therapeutic detail is **extrapolated** from POLD1 and POLD3 disease.

2. **No epidemiology.** No prevalence, incidence, carrier frequency, sex ratio, or geographic data exist beyond "ultra-rare" and a consanguinity association.
3. **Inferred extra-immune mechanism.** The link from replication stress to neurodevelopmental impairment and sensorineural hearing loss is biologically plausible but **not directly demonstrated** at the tissue level.
4. **Variant interpretation is hard.** ClinVar POLD2 entries are overwhelmingly VUS; there is no recurrent, consensus-classified pathogenic CID allele, so diagnosis requires functional validation.
5. **No dedicated animal model** of POLD2-CID and **no disease-specific clinical trials** were identified.
6. **No QOL/prognostic/mortality statistics** specific to POLD2 exist.
7. **Ontology mappings** (several HPO/GO/CL/UBERON terms above) are suggested and should be verified against current ontology releases before database ingestion.

Proposed Follow-up Experiments / Actions

1. **Aggregate cases via GeneMatcher / ESID / inborn-errors-of-immunity registries** to assemble a POLD2 cohort large enough to define penetrance, expressivity, and natural history.
2. **Functional variant pipeline:** Establish a standardized assay (Pol δ -complex stability by co-IP, S-phase/EdU replication-stress readout, dsDNA-break foci, rescue by WT POLD2) to reclassify POLD2 VUS per ACMG functional-evidence criteria (PS3/BS3).
3. **Generate a conditional/hypomorphic *Pold2* mouse** (lymphocyte-specific or patient-equivalent knock-in) to test the replication-stress $\rightarrow$ T-cell-defect causal chain and probe neural/cochlear involvement.
4. **Single-cell immune profiling** (scRNA-seq + TCR-seq) of patient thymic emigrants/peripheral T cells to map where in T-cell development the block occurs and quantify TCR-repertoire restriction.
5. **HSCT outcome registry** for Pol δ -complex deficiencies to formalize reduced-intensity conditioning protocols and quantify DNA-repair-related toxicity.

6. **Audiologic and neurodevelopmental longitudinal follow-up** post-HSCT to determine which deficits are reversible vs. fixed, informing counseling.
 7. **Carrier-screening / prenatal counseling resources** for consanguineous families, including cascade-testing workflows once a familial POLD2 variant is identified.
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Report compiled from a 5-iteration autonomous investigation (9 confirmed findings; 28 papers reviewed). Evidence types: predominantly human clinical case reports and in vitro functional studies, with population-genetic constraint data (gnomAD) and cross-disorder analogy to POLD1/POLD3 deficiencies.

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