Severe Congenital Neutropenia 9 (SCN9): A Comprehensive Disease Characterization

Disease: Severe Congenital Neutropenia 9 (SCN9) **MONDO ID:** MONDO:0030726 · **OMIM:** 619813 · **Gene:** *CLPB* (SKD3; HGNC:30664) **Category:** Mendelian (autosomal dominant)

Summary

Severe Congenital Neutropenia 9 (SCN9) is a rare, autosomal-dominant inborn error of granulopoiesis caused by **heterozygous, dominant-negative missense variants in *CLPB*** (also called SKD3), a gene on chromosome 11q13.4 encoding a mitochondrial intermembrane-space (IMS) AAA+ ATPase that functions as a protein **disaggregase/refoldase**. The disease was formally delineated in 2021–2022 when two groups independently showed that monoallelic *CLPB* variants, clustering near the ATP-binding pocket, poison the wild-type CLPB oligomer and impair its disaggregase activity — a true dominant-negative mechanism rather than haploinsufficiency (PMID: 34115842; PMID: 34140661). This molecular lesion blocks granulocytic differentiation of hematopoietic progenitors and increases apoptosis of neutrophil precursors, producing a fully penetrant myeloid maturation arrest and severe neutropenia with recurrent bacterial infections beginning in infancy.

A central theme of this disease is its **zygosity-dependent severity spectrum**. The same gene, *CLPB*, causes two distinct Mendelian disorders: the **monoallelic (dominant) form** described here — SCN9 — which is typically **isolated severe neutropenia**; and a **biallelic (recessive) form** (OMIM 616271; 3-methylglutaconic aciduria type VII) that combines neutropenia with 3-methylglutaconic aciduria (3-MGA), cataracts, progressive brain atrophy, intellectual disability, movement disorder, epilepsy, and high early-childhood mortality. Critically, the metabolic hallmark 3-MGA-uria is characteristically **absent** in SCN9 (0/5 tested cases), and the monoallelic form carries a substantially better prognosis (4-year survival ~82% vs ~50% for biallelic disease).

Management parallels other severe congenital neutropenias: **granulocyte colony-stimulating factor (G-CSF)** maintains protective neutrophil counts and reduces infections, while **allogeneic hematopoietic stem cell transplantation (HSCT)** remains the only curative option, reserved for G-CSF non-response or malignant (MDS/AML) transformation. Mechanistic work in cellular models points to **ROS-driven apoptosis** at the onset of differentiation, with experimental rescue by antioxidants (N-acetylcysteine), free fatty acids, or citrate — candidate future metabolic therapies. This report synthesizes 10 confirmed findings across 34 reviewed papers into a full, section-by-section disease knowledge base entry.

Key Findings

Finding 1 — SCN9 is caused by heterozygous dominant-negative *CLPB* variants (autosomal dominant)

SCN9 maps to **MONDO:0030726** ("Neutropenia, severe congenital, 9, autosomal dominant"), cross-referenced to **OMIM:619813**, **UMLS:C5676954**, and **GARD:0025625**, with material basis in germline mutation in ***CLPB*** (HGNC:30664). The defining study, Warren et al. 2022 (*Blood*), used exome sequencing of 104 persons with congenital neutropenia to identify heterozygous missense *CLPB* variants in 5 severe congenital neutropenia cases, with 5 additional cases identified through supplementary sequencing — 10 total. The variants are not scattered but **cluster near the adenosine-triphosphate–binding pocket** of CLPB.

> "Exome sequencing of 104 persons with congenital neutropenia identified heterozygous missense variants of CLPB (caseinolytic peptidase B) in 5 severe congenital neutropenia cases, with 5 more cases identified through additional sequencing efforts or clinical sequencing." — PMID: 34115842
>
> "the CLPB variants are distinct, consisting of heterozygous variants that cluster near the adenosine triphosphate-binding pocket" — PMID: 34115842

This dominant form is molecularly and clinically distinct from the biallelic *CLPB* disease (OMIM 616271, 3-MGA-uria type VII, autosomal recessive).

Finding 2 — Mechanism: dominant-negative CLPB impairs mitochondrial disaggregase activity, blocking granulopoiesis and increasing apoptosis

CLPB (SKD3) is an **AAA+ ATPase disaggregase/refoldase** residing in the **mitochondrial intermembrane space (IMS)**. SCN9 variants physically **associate with wild-type CLPB and inhibit both its ATPase and disaggregase activities in a dominant-negative fashion**. Both genetic loss of CLPB and expression of the variant protein impair granulocytic differentiation of human hematopoietic progenitors and increase apoptosis.

> "These CLPB variants associate with wild-type CLPB and inhibit its adenosine triphosphatase and disaggregase activity in a dominant-negative fashion." — PMID: 34115842
>
> "Both genetic loss of CLPB and expression of CLPB variants result in impaired granulocytic differentiation of human hematopoietic progenitor cells and increased apoptosis." — PMID: 34115842

A key mechanistic link is to **HAX1**, the protein mutated in SCN3 (Kostmann disease). CLPB maintains the solubility of HAX1, and HAX1 in turn acts as a direct stimulatory cofactor that oligomerizes and activates CLPB — tying two distinct neutropenia genes into one IMS proteostasis axis.

> "loss of function in either gene causes severe congenital neutropenia as well as neuropathology and causes many proteins in the IMS and its bounding membranes to become insoluble" — PMID: 42244541

In CLPB-deficient myeloblasts, the downstream picture is reduced mitochondrial membrane potential, insoluble HAX1 aggregates, and ROS-driven apoptosis precisely at the onset of G-CSF-induced differentiation (PMID: 39644357). Monoallelic variants disturb refoldase activity (and to a lesser extent ATPase activity) dominant-negatively (PMID: 34140661).

Finding 3 — SCN9 phenotype is typically isolated severe neutropenia, lacking the neuro/metabolic features of biallelic disease

In Warren et al. 2022, heterozygous *CLPB* carriers had severe congenital neutropenia but — unlike biallelic disease — **3-methylglutaconic aciduria was not observed**, and syndromic features (cataracts, neurological disease) were uncommon.

> "3-methylglutaconic aciduria was not observed and, other than neutropenia, these clinical features were uncommon in our series" — PMID: 34115842

By contrast, the biallelic recessive syndrome (OMIM 616271) spans a neurological phenotype from nonprogressive intellectual disability to prenatal encephalopathy:

> "a neurological phenotype ranging from nonprogressive intellectual disability to a prenatal encephalopathy with progressive brain atrophy, movement disorder, cataracts, and early death" — PMID: 25597510

A subset of monoallelic (de novo) cases do show some neurodevelopmental involvement (seizures, developmental delay), indicating a phenotypic spectrum rather than a clean dichotomy (PMID: 34140661).

Finding 4 — Zygosity predicts outcome: monoallelic disease is milder with better survival

Heath et al. 2026 assembled a cohort of **63 individuals (41 biallelic, 22 monoallelic)** and quantified the zygosity-outcome relationship.

> "Death occurred in 66% of biallelic and 23% of monoallelic individuals, with earlier median age at death in biallelic cases (6 months vs 2.4 years). Biallelic cases had significantly higher DBI scores and poorer survival (4-year survival: 50% vs 82%)." — PMID: 41719910

Notably, **structural predictions** (nonsense-mediated decay or ankyrin-repeat-domain disruption) were stronger predictors of survival than zygosity or age of onset alone, and stop/stop genotypes conferred greater disease burden than missense combinations. Early onset (<12 months) correlated with more severe progression.

Finding 5 — Treatment: G-CSF maintains counts and reduces infections; HSCT is definitive; antioxidant/metabolic rescue is experimental

In a CLPB-neutropenia case report, intermittent G-CSF successfully maintained protective neutrophil counts and cut respiratory infections:

> "Administration of granulocyte colony-stimulating factor successfully maintained neutrophil counts above 0.5 × 109/L and significantly reduced the frequency of respiratory tract infections." — PMID: 41560087

Across congenital neutropenia syndromes, G-CSF responders retain residual risk of bone marrow failure, MDS, and AML (PMID: 38589208); HSCT is the only curative option for transformation or G-CSF non-response (PMID: 15640815; PMID: 15489867). Mechanistic rescue experiments identify candidate metabolic strategies:

> "N-acetylcysteine, exogenous free fatty acids, or exogenous citrate protected CLPB-deficient 32Dcl3 cells from apoptosis at the onset of differentiation" — PMID: 39644357

Finding 6 — Model systems: zebrafish morphant, CLPB-KO 32Dcl3 myeloblasts, cross-species orthology

The zebrafish *clpb* morphant recapitulates the CNS phenotype of the recessive syndrome, with rescue specificity establishing variant pathogenicity:

> "Suppression of clpb in zebrafish embryos induced a central nervous system phenotype that was consistent with cerebellar and cerebral atrophy that could be rescued by wild-type, but not mutant, human CLPB mRNA" — PMID: 25597510

The most neutropenia-relevant model is the **CRISPR CLPB-knockout of the IL-3-dependent mouse 32D clone 3 (32Dcl3) myeloblastic line**, which reproduces the differentiation/apoptosis defect:

> "we used 32D clone 3 (32Dcl3) cells, an interleukin-3 (IL-3)-dependent mouse myeloblastic cell line model, to investigate the effects of CLPB knockout on myeloblast-to-neutrophil differentiation" — PMID: 39644357

Finding 7 — Inheritance & population genetics: AD via de novo dominant-negative missense; CLPB is LoF-tolerant

SCN9 arises through de novo monoallelic missense variants acting dominant-negatively:

> "we identified one of four different de novo monoallelic missense variants in CLPB. We show that these variants disturb refoldase and to a lesser extent ATPase activity of CLPB in a dominant-negative manner" — PMID: 34140661

Critically, **gnomAD constraint metrics exclude haploinsufficiency**: pLI ≈ 2.4×10^{-5}, observed/expected LoF = 40/78.4 (oe_lof 0.51, LOEUF 0.66), missense Z = 1.53 — i.e., heterozygous loss-of-function is tolerated. This confirms that disease requires a *poison* (dominant-negative) allele, not simple gene-dosage reduction. The biallelic form shows a Greenlandic founder cohort:

> "Four of the individuals were of Greenlandic descent, and one was North American" — PMID: 25597511

Finding 8 — Diagnostics & anatomy: severe neonatal neutropenia with marrow maturation arrest; diagnosis by NGS/WES

Severe congenital neutropenia is defined hematologically by myeloid maturation arrest:

> "characterized by a maturation arrest of myelopoiesis at the promyelocyte/myelocyte stage of development. This arrest results in severe neutropenia with absolute neutrophil counts (ANC) less than 0.2 x 10(9)/l associated with severe systemic bacterial infections from early infancy" — PMID: 10994541

Molecular diagnosis of CLPB-SCN relies on NGS gene panels / whole-exome or whole-genome sequencing; *CLPB* is now routinely included on congenital neutropenia panels (PMID: 40510848; PMID: 41383606), and reanalysis of previously negative exomes can reveal *CLPB* (PMID: 41560087).

Finding 9 — Downstream consequences & complications: IMS proteostasis collapse, infection susceptibility, MDS/AML risk

CLPB loss triggers stress-specific IMS protein aggregation that cripples mitochondrial quality control:

> "CLPB deficiency impeding SPY complex function by virtue of protein aggregation in the intermembrane space" — PMID: 38270563

Clinically, the neutropenia drives recurrent severe bacterial infections, and like other SCN subtypes carries malignant transformation risk:

> "neutropenia that can develop into leukemia" — PMID: 25597510

Finding 10 — Official HPO phenotype frequencies for SCN9

The HPO disease annotation for OMIM:619813 (source P 34115842, n≈10) formalizes the phenotype frequencies, with the 0/5 for 3-MGA-uria confirming the metabolic hallmark of biallelic disease is absent in SCN9.

> "3-methylglutaconic aciduria was not observed and, other than neutropenia, these clinical features were uncommon in our series" — PMID: 34115842

HPO term	ID	Frequency in SCN9
Myeloid maturation arrest	HP:0410253	10/10 (100%)
Infantile onset	HP:0003593	5/10
Childhood onset	HP:0011463	4/10
Congenital onset	HP:0003577	1/10
Cataract	HP:0000518	2/10 (20%)
Splenomegaly	HP:0001744	2/10
Seizure	HP:0001250	2/10
Global developmental delay	HP:0001263	1/10
3-Methylglutaconic aciduria	HP:0003535	0/5 (0%)
Autosomal dominant inheritance	HP:0000006	—

Full Section-by-Section Report

1. Disease Information

SCN9 is a rare Mendelian disorder of granulopoiesis producing severe, persistent neutropenia from early infancy, caused by heterozygous dominant-negative variants in *CLPB*. Key identifiers: **MONDO:0030726**, **OMIM:619813**, **UMLS:C5676954**, **GARD:0025625**. It falls under the broader ICD-10 category D70 (neutropenia) / ICD-11 4B00.0 (congenital neutropenia); MeSH maps to "Congenital Bone Marrow Failure Syndromes" / "Neutropenia." **Synonyms/alternative names:** Severe congenital neutropenia type 9; autosomal dominant *CLPB*-related neutropenia; CLPB-associated congenital neutropenia (monoallelic form). The information is derived primarily from aggregated disease-level resources (OMIM, Orphanet, HPO) and from small published case series/cohorts (Warren 2022, Wortmann 2021, Heath 2026) rather than from EHR.

2. Etiology

Primary cause — genetic: heterozygous (monoallelic) missense variants in *CLPB*/SKD3 that cluster near the ATP-binding pocket and act in a dominant-negative manner (PMID: 34115842; PMID: 34140661). Many arise **de novo**. **Genetic risk factors:** the causal variant is the sole established risk factor; no susceptibility loci or modifier genes are established for the dominant form, though structural impact (NMD vs ankyrin-domain disruption) modifies severity in the broader CLPB spectrum (PMID: 41719910). **Environmental risk/protective factors:** none identified — this is a monogenic disorder. **Gene–environment interactions:** none established; infection exposure determines clinical severity of complications but does not cause the disease.

3. Phenotypes

The core phenotype is a **laboratory/hematologic abnormality** — severe neutropenia (ANC often <0.2–0.5×10^9/L) with bone-marrow myeloid maturation arrest (HP:0410253, 100%) — manifesting clinically as **recurrent severe bacterial infections** (HP:0002718) from early infancy. Onset is congenital/infantile (HP:0003593/HP:0003577). Severity is severe; course is chronic and lifelong but stabilizable with G-CSF. Non-hematologic features (cataract HP:0000518 20%; splenomegaly HP:0001744; seizure HP:0001250) occur at low frequency; 3-MGA-uria (HP:0003535) is characteristically absent (0/5). **Quality-of-life impact:** chronic infection susceptibility, repeated hospitalization, need for lifelong G-CSF injections and infection prophylaxis; well-managed patients can achieve good functional status, but transformation to MDS/AML is a severe QoL and survival threat.

4. Genetic / Molecular Information

Causal gene: *CLPB* (SKD3), HGNC:30664, OMIM gene 616254, Entrez 81570, Ensembl ENSG00000162129, UniProt Q9H078, locus **11q13.4** (GRCh38 chr11:72,285,495–72,434,680). **Pathogenic variants:** heterozygous **missense** variants near the ATP-binding pocket (dominant SCN9); biallelic missense/frameshift/nonsense (recessive 3-MGA-uria VII). Example recessive variants: c.1016delT (p.L339Rfs*5), c.1087A>G (p.R363G) (PMID: 37906145); p.Arg408Gly abolishes ATPase function (PMID: 25597510). Classification: pathogenic/likely pathogenic per ACMG. Allele frequency: ultra-rare; gnomAD shows CLPB is LoF-tolerant (oe_lof 0.51, LOEUF 0.66), excluding haploinsufficiency. Origin: germline. Functional consequence: dominant-negative (SCN9) vs loss-of-function (recessive disease). Modifier genes: none validated; structural class of the variant is the main severity modifier. Epigenetic/chromosomal abnormalities:* none described.

5. Environmental Information

Not applicable as a cause — SCN9 is monogenic. Environmental **triggers of complications** include bacterial and viral pathogens (recurrent sepsis, respiratory/skin/oral infections; EBV reactivation has been reported in the CLPB/VPS45 neutropenia spectrum). No toxins, lifestyle, or occupational exposures contribute to disease causation.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. A **heterozygous dominant-negative missense variant in *CLPB*** (near the ATP-binding pocket) **leads to** a mutant CLPB subunit that is translated and imported into the mitochondrial IMS.
2. The mutant subunit **co-assembles with wild-type CLPB** into mixed oligomers and **inhibits** the complex's ATPase and disaggregase/refoldase activity (dominant-negative poisoning) — *demonstrated biochemically* (PMID: 34115842).
3. Loss of disaggregase activity **results in** failure to maintain solubility of IMS clients — notably **HAX1 aggregation** — and impairment of the proteolytic **SPY complex (STOML2–PARL–YME1L1)** (PMID: 42244541; PMID: 38270563).
4. IMS proteostasis collapse **leads to** reduced mitochondrial membrane potential and **ROS accumulation** in myeloid precursors (PMID: 39644357).
5. ROS/stress **triggers apoptosis specifically at the onset of G-CSF–induced granulocytic differentiation**, i.e., CLPB is a pro-survival factor at this checkpoint (PMID: 39644357).
6. Precursor apoptosis **produces** myeloid maturation arrest at the promyelocyte/myelocyte stage → **severe peripheral neutropenia** → **recurrent bacterial infections** from infancy.
7. *Branch (downstream, inferred):* chronic proliferative stress on the marrow **contributes to** clonal evolution and **MDS/AML transformation** risk, as in other SCN subtypes.

Molecular pathways: mitochondrial protein quality control / disaggregation; HAX1–CLPB axis; SPY proteolytic complex. **Cellular processes:** apoptosis (GO:0006915), response to ROS (GO:0000302), neutrophil differentiation (GO:0030223), protein refolding/disaggregation (GO:0042026). **Protein dysfunction:** dominant-negative impairment of an AAA+ ATPase disaggregase. **Cell types:** neutrophil (CL:0000775), promyelocyte (CL:0000836), granulocyte-monocyte progenitor (CL:0000557), hematopoietic stem cell (CL:0000037). **Subcellular:** mitochondrial intermembrane space (GO:0005758). CLPB assembles into homo-tetradecamers (apo) / homo-dodecamers (substrate-bound) with an essential N-terminal ankyrin-repeat domain (PMID: 36745679).

7. Anatomical Structures Affected

Organ level: bone marrow (UBERON:0002371) and blood (UBERON:0000178) are primary; spleen (splenomegaly in some) secondary. **Body system:** hematopoietic/immune. **Cell level:** neutrophils and their myeloid precursors (promyelocytes, GMPs, HSCs). **Subcellular:** mitochondria, specifically the intermembrane space (GO:0005758). **Lateralization:** not applicable (systemic hematologic disease). In the biallelic form, additional organs are involved — CNS (UBERON:0000955, brain atrophy), lens/eye (cataract), and ovary (premature ovarian insufficiency, PMID: 36074910).

8. Temporal Development

Onset: congenital/neonatal to infantile; neutropenia detectable from early infancy. **Onset pattern:** chronic from birth. **Progression:** generally stable neutropenia maintainable with G-CSF; risk of progression to marrow failure or MDS/AML over time. Early onset (<12 months) predicts more severe progression across the CLPB spectrum (PMID: 41719910). **Course:** chronic, lifelong. **Remission:** treatment-induced count normalization with G-CSF; no spontaneous cure. **Critical period:** the onset of granulocytic differentiation is the vulnerable checkpoint (where CLPB-dependent apoptosis occurs), and infancy is the window of greatest infection risk.

9. Inheritance and Population

Inheritance: autosomal dominant (SCN9, OMIM 619813), frequently de novo, dominant-negative (PMID: 34140661). **Penetrance:** myeloid maturation arrest appears fully penetrant (100%) in reported carriers; expressivity variable for non-hematologic features. **Epidemiology:** ultra-rare — dozens of families worldwide; the largest CLPB cohort assembled only 63 individuals across both zygosity forms (PMID: 41719910). **Founder effects:** a Greenlandic founder cohort exists for the biallelic form (PMID: 25597511); consanguinity enriches the recessive disease. **Carrier frequency:** not established (dominant form typically de novo). **Sex ratio:** both sexes affected, no strong skew. **Age distribution:** presents in infancy.

10. Diagnostics

Hematology: CBC showing severe neutropenia (ANC <0.2–0.5×10^9/L); bone marrow aspirate showing promyelocyte/myelocyte maturation arrest (PMID: 10994541). **Genetic testing (definitive):** NGS congenital-neutropenia gene panels, WES, or WGS, now including *CLPB*; reanalysis of prior negative exomes is warranted (PMID: 40510848; PMID: 41383606; PMID: 41560087). **Supportive discriminators:** urine organic acids (3-MGA — normal in SCN9,

elevated in biallelic disease; CHEBI:1890), slit-lamp exam (cataract), neuro-exam/MRI (recessive syndrome). **Differential diagnosis:** other SCN genes — *ELANE* (SCN1), *GFI1* (SCN2), *HAX1* (SCN3/Kostmann), *G6PC3* (SCN4), *VPS45* (SCN5), *CSF3R* (SCN7), *SRP54* (SCN8), *JAGN1*, *WAS* — plus Shwachman-Diamond and cyclic neutropenia. **Screening:** no population newborn screening; cascade family genetic testing applies once a variant is known.

11. Outcome / Prognosis

Survival: monoallelic (SCN9) ~82% 4-year survival vs ~50% biallelic; death in 23% monoallelic vs 66% biallelic; median age at death 2.4 years (monoallelic) vs 6 months (biallelic) (PMID: 41719910). **Morbidity:** recurrent infections, hospitalizations; complications include sepsis, oral/periodontal and respiratory infections, hypersplenism, and MDS/AML transformation. **Recovery potential:** neutropenia is controllable (not curable) with G-CSF; HSCT can cure. **Prognostic factors:** zygosity, variant structural class (NMD/ankyrin-domain disruption > zygosity as predictor), age of onset (<12 months worse), disease burden index.

12. Treatment

Pharmacotherapy: G-CSF / filgrastim (NCIT:C1705-class) is first-line, maintaining ANC >0.5×10^9/L and reducing infections (PMID: 41560087); pathogen-directed **antibiotics** (NCIT:C15847) for infections. **Advanced therapeutics: allogeneic HSCT** (NCIT:C15431) is the only curative option, indicated for G-CSF non-response, marrow failure, or MDS/AML (PMID: 15640815; PMID: 15489867). **Experimental/metabolic:** N-acetylcysteine (NCIT:C291), free fatty acids, or citrate rescued CLPB-deficient myeloblasts from apoptosis in vitro (PMID: 39644357) — candidate antioxidant/metabolic strategies not yet clinically validated. **Supportive care:** infection prophylaxis, prompt treatment of febrile episodes, dental/periodontal care. **Pharmacogenomics / gene therapy / RNA therapy:** none established.

13. Prevention

No primary prevention exists for this monogenic disease. **Secondary prevention:** early genetic diagnosis enabling prompt G-CSF and infection surveillance; routine monitoring for MDS/AML (serial CBC, marrow exams). **Tertiary prevention:** infection prophylaxis, timely HSCT before leukemic progression. **Genetic counseling:** autosomal dominant recurrence risk (often de novo); prenatal/preimplantation testing possible once the familial variant is known. **Immunization/public health/environmental interventions:** not applicable to disease causation (standard vaccination and infection control apply to the immunocompromised patient).

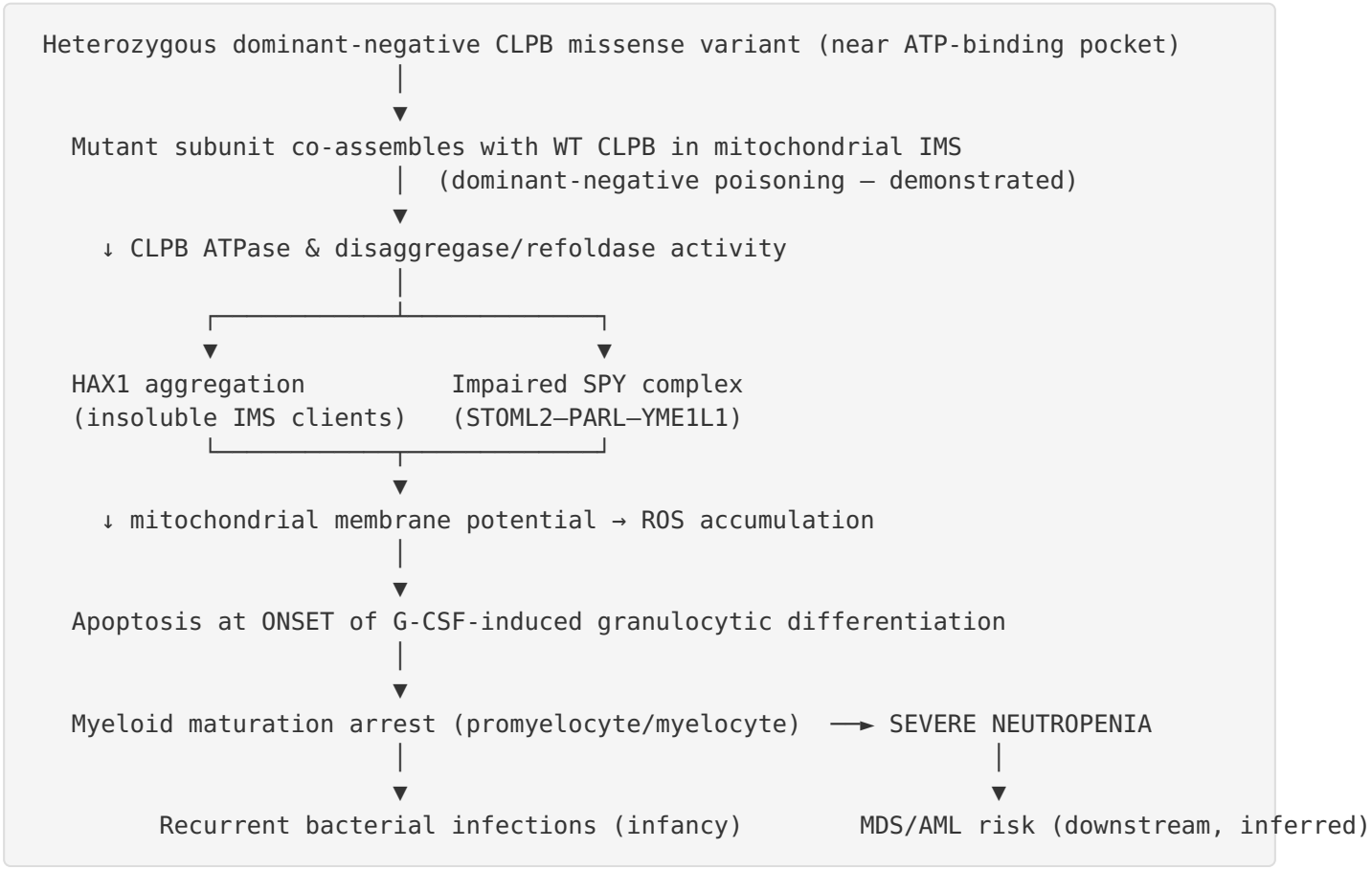
14. Other Species / Natural Disease

CLPB is evolutionarily conserved in the **ClpB/Hsp100 AAA+ disaggregase family**, with a bacterial ClpB homolog. **Orthologs (NCBI Gene):** mouse *Clpb* (GeneID 20480), rat *Clpb* (65041), zebrafish *clpb* (100331587); human *CLPB* Entrez 81570. No naturally occurring companion-animal or wildlife disease is documented (no OMIA entry noted). No zoonotic potential. The deep conservation of the disaggregase mechanism underpins the utility of zebrafish and rodent/cellular models.

15. Model Organisms

Zebrafish: morpholino *clpb* knockdown produces cerebellar/cerebral atrophy, rescued by wild-type but not mutant human *CLPB* mRNA — validating variant pathogenicity (PMID: 25597510). **Cellular:** CRISPR CLPB-knockout of IL-3-dependent mouse **32Dcl3 myeloblasts** recapitulates the neutropenia-relevant defect — reduced mitochondrial membrane potential, insoluble HAX1 aggregates, ROS-driven apoptosis at G-CSF-induced differentiation (PMID: 39644357). **Biochemical reconstitution:** purified human CLPB + HAX1 systems (PMID: 42244541) and cryo-EM structural models (PMID: 36745679). **Phenotype recapitulation:** zebrafish captures the neurological (recessive) phenotype; 32Dcl3 captures the myeloid differentiation defect. **Limitations:** no dedicated mouse model of the dominant SCN9 phenotype is yet reported; morphant models have known off-target caveats.

Mechanistic Model / Interpretation



Zygosity–mechanism–outcome synthesis:

Feature	Monoallelic (SCN9, AD)	Biallelic (3-MGA-uria VII, AR)
OMIM	619813	616271
Mechanism	Dominant-negative missense	Loss of function (biallelic)
Neutropenia	Yes (100% maturation arrest)	Yes
3-MGA-uria	Absent (0/5)	Characteristic
Cataracts / CNS / movement disorder	Uncommon	Frequent
4-year survival	~82%	~50%
Median age at death	2.4 years	6 months

The unifying insight is that *CLPB* sits at the heart of a **mitochondrial IMS proteostasis network** linking it to **HAX1** (SCN3/Kostmann) — explaining why two genetically distinct congenital neutropenias converge on the same disaggregase pathway. gnomAD LoF-tolerance proves that one functional allele suffices for neutrophil production; disease in SCN9 therefore requires an actively interfering allele, and the poisoned oligomer tips neutrophil precursors into ROS-driven apoptosis at their most vulnerable differentiation checkpoint.

Evidence Base

PMID	Title / Focus	Role in this report
34115842	*Heterozygous variants of CLPB are a cause of severe congenital neutropenia*	**Defining paper**; dominant-negative mechanism, phenotype, HPO frequencies
34140661	*Neutropenia and intellectual disability are hallmarks of biallelic and de novo CLPB deficiency*	De novo dominant-negative inheritance; refoldase>ATPase defect
41719910	*From genotype to outcome: zygosity-specific insights in 63 cases*	Quantitative survival/outcome by zygosity
39644357	*Mitochondrial CLPB is a pro-survival factor at onset of granulocytic differentiation*	32Dcl3 model; ROS apoptosis; NAC/FFA/citrate rescue
42244541	*HAX1 drives assembly and activation of CLPB*	CLPB–HAX1 axis; IMS insolubility
38270563	*CLPB dysfunction impacts the proteolytic SPY complex*	Downstream IMS proteostasis collapse
25597510	*CLPB mutations cause 3-MGA-uria, brain atrophy...*	Biallelic phenotype; zebrafish model; leukemia risk
25597511	*CLPB variants — AR mitochondrial disorder*	Greenlandic founder effect
41560087	*CLPB deficiency-associated congenital neutropenia: case report*	G-CSF efficacy; exome reanalysis
10994541	*Severe congenital neutropenia: diagnosis & therapy*	SCN diagnostic definition
36745679	*Structural characterization of human CLPB disaggregase*	Oligomerization; ankyrin domain
38589208	*Clinicopathological features of congenital neutropenia syndromes*	MDS/AML risk; differential diagnosis
15640815, 15489867	HSCT in SCN	Curative transplant evidence
		Genetic diagnostic approach

PMID	Title / Focus	Role in this report
40510848, 41383606	WES/WGS & national neutropenia screening	
36074910	*POI in CLPB deficiency*	Adult/ovarian complication (biallelic)

Limitations and Knowledge Gaps

1. **Very small sample sizes.** The disease rests on ~10 heterozygous cases (Warren 2022) and a combined cohort of 63 across both zygosity forms (Heath 2026). HPO frequencies (e.g., cataract 2/10) have wide confidence intervals.
2. **No dedicated dominant-model organism.** Mechanistic data derive from CLPB-knockout cell lines and morphant zebrafish that model loss of function/recessive phenotypes, not the dominant-negative SCN9 state specifically.
3. **Spectrum vs dichotomy.** Some monoallelic cases show neurodevelopmental features, blurring the clean "isolated neutropenia" picture; genotype–phenotype rules remain incompletely defined.
4. **No validated epidemiologic prevalence/incidence** for SCN9 specifically (ultra-rare; registry data limited).
5. **Metabolic/antioxidant rescue is in vitro only** — NAC, FFA, and citrate have not been tested clinically.
6. **Leukemic transformation risk is extrapolated** from SCN broadly; CLPB-specific transformation rates are not quantified.

Proposed Follow-up Experiments / Actions

1. **Generate a knock-in mouse** carrying a human SCN9 dominant-negative *CLPB* missense allele to establish an in-vivo dominant model and quantify neutrophil, survival, and MDS/AML outcomes.

2. **Prospective natural-history registry** for CLPB-neutropenia to firm up prevalence, penetrance, transformation rates, and genotype–phenotype correlations (expanding the Heath 2026 cohort).
3. **Preclinical trial of antioxidant/metabolic rescue** (N-acetylcysteine, citrate, free fatty acids) in CLPB-deficient primary human $CD34^+$ progenitors and the knock-in mouse, moving toward a pilot clinical study.
4. **Structural/biochemical dissection** of how each variant class (ATP-pocket missense vs ankyrin-domain disruption) poisons the oligomer, to build a variant-to-severity predictor usable in counseling.
5. **Longitudinal MDS/AML surveillance protocol** specific to CLPB-SCN, correlating clonal markers (e.g., *CSF3R*/*RUNX1* mutations) with transformation.
6. **Systematic HAX1–CLPB interaction mapping** in patient-derived cells to test whether HAX1 stabilization can bypass the CLPB defect therapeutically.

Evidence source types represented: human clinical (cohorts/case reports), model organism (zebrafish), in vitro (32Dcl3 knockout, biochemical reconstitution, cryo-EM), and computational (gnomAD constraint, structural prediction).
