

DNASE2 Deficiency (Autoinflammatory–Pancytopenia Syndrome, AIPCS): Comprehensive Disease Characteristics Report

Disease: DNASE2 Deficiency / Autoinflammatory–Pancytopenia Syndrome (AIPCS) **MONDO:** MONDO:0800132 · **OMIM:** #619858 · **Category:** Mendelian (autosomal recessive)

Evidence base: This is an ultra-rare disease with a small primary human literature (first described 2017). Mechanistic depth comes largely from mouse genetics, which recapitulate the human phenotype well. Evidence-source types are flagged throughout as [human], [mouse], [in vitro], or [computational].

Summary

DNASE2 deficiency — formally designated **Autoinflammatory–Pancytopenia Syndrome (AIPCS; MONDO:0800132, OMIM #619858)** — is an ultra-rare, autosomal-recessive monogenic **type I interferonopathy** caused by biallelic loss-of-function variants in *DNASE2* (chromosome 19p13.13). The gene encodes **DNase II-alpha**, a 360-amino-acid ubiquitously expressed lysosomal acid endonuclease that degrades DNA derived from apoptotic cells and from nuclei expelled by erythroblasts during definitive erythropoiesis. When this enzyme is lost, undegraded self-DNA accumulates within macrophage lysosomes and leaks to the cytosol, where it is sensed by the **TLR-independent cGAS–STING–TBK1–IRF3/7** axis. The result is constitutive overproduction of type I interferon (principally IFN- β), accompanied by a separable TNF- α -driven inflammatory program, which together produce a congenital/neonatal-onset multisystem autoinflammatory disease.

The core human phenotype, first defined by Rodero et al. in 2017, comprises severe neonatal anemia, membranoproliferative glomerulonephritis, liver fibrosis, deforming arthropathy, and anti-DNA antibodies, all on a background of a strong blood interferon signature and constitutive STAT1/STAT3 phosphorylation. Subsequent case reports have expanded the spectrum to include an extremely severe antenatal presentation (fetal hydrops, intrauterine growth restriction, cardiomyopathy, persistent pancytopenia, hepatosplenomegaly, cholestatic jaundice, and hemophagocytic lymphohistiocytosis-like features with marked hyperferritinemia), as well as recurrent fevers, vasculitic skin lesions/chilblains, gastrointestinal inflammation, lipodystrophy, and subcortical white-matter lesions.

The disease mechanism is exceptionally well validated by *Dnase2*-null mouse genetics: embryonic lethality from IFN- β -driven lethal anemia is rescued by crossing onto an *Ifnar*-null background, sensing is TLR-independent, and the surviving mice develop a chronic, TNF- α -dependent, rheumatoid-arthritis-like polyarthritis driven in part by IFN- γ -producing Th1 cells independent of type I IFN. Diagnosis rests on the blood interferon signature, reduced DNase II enzymatic activity, and exome/genome sequencing. Mechanism-directed treatment centers on **JAK1/2 inhibitors** (baricitinib, ruxolitinib) to suppress IFN signaling, with a strong preclinical rationale for anti-TNF therapy against the arthritis component and hematopoietic stem-cell transplantation as a conceptual cure.

Key Findings

F001 — DNASE2 deficiency is an autosomal-recessive type I interferonopathy caused by biallelic loss-of-function *DNASE2* variants [human]

The defining human study is Rodero et al. (2017), which identified biallelic *DNASE2* mutations in three patients from two families, each with loss of DNase II endonuclease activity, elevated IFN- α protein measured by digital ELISA, enhanced interferon signaling on RNA-Seq, and constitutive upregulation of phosphorylated STAT1 and STAT3 in patient lymphocytes and monocytes. In the authors' words: *"In both families we identify biallelic mutations in DNASE2, associated with a loss of DNase II endonuclease activity. We record increased interferon alpha protein levels using digital ELISA, enhanced interferon signaling by RNA-Seq analysis and constitutive upregulation of phosphorylated STAT1 and STAT3 in patient lymphocytes and monocytes"* [PMID: 29259162](#). Subsequent reports confirmed additional biallelic/homozygous pathogenic variants, including a proximal intronic splice-site variant causing type I interferon-

mediated autoinflammation in two unrelated patients [PMID: 41472683](#), which describes DNase II as "*a lysosomal endonuclease critical for degrading DNA during erythropoiesis and apoptosis*" and confirms recessive biallelic loss-of-function inheritance. This establishes the disease as a monogenic, recessive interferonopathy with a clear molecular signature.

F002 — Core clinical phenotype: neonatal anemia, membranoproliferative glomerulonephritis, liver fibrosis, deforming arthropathy, and anti-DNA antibodies [human]

The index cohort variably demonstrated a stereotyped multisystem picture: "*we identify two siblings and a singleton variably demonstrating severe neonatal anemia, membranoproliferative glomerulonephritis, liver fibrosis, deforming arthropathy and increased anti-DNA antibodies*" [PMID: 29259162](#). Peripheral blood showed increased erythroblasts and a hematological-disease transcriptomic signature, linking the anemia directly to the enzyme's erythropoietic role. The 2026 Omani neonatal report expanded the severe end of the spectrum, with disease "*manifesting antenatally with fetal hydrops, intrauterine growth restriction, and cardiomyopathy. Postnatally, the infant developed persistent pancytopenia, hepatosplenomegaly, cholestatic jaundice, and hemophagocytic lymphohistiocytosis-like features, including marked hyperferritinemia*" [PMID: 42491852](#).

F003 — Mechanism: undegraded self-DNA drives cGAS–STING-dependent type I IFN, with an IFNAR-independent inflammatory branch [mouse, in vitro]

Mouse genetics establish an unambiguous causal chain. *Dnase2*-null embryos accumulate undigested DNA in macrophages and die in utero from IFN- β -driven lethal anemia; crucially, "*When the DNase II-deficient mice were crossed with mice deficient in type I interferon receptor, the resultant 'double-mutant' mice were born healthy*" [PMID: 15568025](#), proving type I IFN signaling via IFNAR is causally required for lethal anemia. Sensing is TLR-independent: "*The ablation of Toll-like receptor (TLR) 3 and 9, or their adaptor molecules (MyD88 and TRIF), had no effect on the lethality of the DNase II(-/-) mice. These results indicate that there is a TLR-independent sensing mechanism*" [PMID: 16301743](#), implicating cytosolic cGAS–STING. This is confirmed functionally: DNase2-deficient patient fibroblasts have a constitutively primed cGAS–STING–TBK1 pathway [PMID: 33916318](#). A type I IFN-independent branch also contributes — in *Dnase2/Ifnar* double-knockout mice, chronic polyarthritis is driven by IFN- γ -producing Th1 cells [PMID: 31464028](#) — and STING contributes to paradoxical ectopic bone formation [PMID: 27740718](#).

F004 — DNase II acts non-cell-autonomously in macrophages to degrade erythroid-expelled nuclear DNA; it is essential for definitive erythropoiesis [mouse]

Kawane et al. (2001) showed that DNase II-null mice are not born, dying of severe anemia, and that transfer of mutant fetal liver cells into irradiated wild-type mice generated mature red blood cells, demonstrating a non-cell-autonomous mechanism. Histochemistry localized the critical enzyme source: *"the critical cellular sources of DNase II are macrophages present at the site of definitive erythropoiesis in the fetal liver. Thus, DNase II in macrophages appears to be responsible for destroying the nuclear DNA expelled from erythroid precursor cells"* [PMID: 11375492](#). This directly explains the anemia: central nurse macrophages in erythroblastic islands normally phagocytose and digest the extruded erythroblast nucleus, and without DNase II this DNA accumulates and triggers IFN.

F005 — Two-branch mechanism: IRF3/7-dependent IFN- β drives embryonic anemia; TNF- α drives chronic polyarthritis (IFN-independent) [mouse]

Kawane et al. (2006) found that *Dnase2^{-/-} Ifnar^{-/-}* mice (and mice with induced DNase II deletion) develop chronic, destructive polyarthritis resembling rheumatoid arthritis, with high serum anti-CCP antibody, rheumatoid factor, and MMP-3. *"Early in the pathogenesis, expression of the gene encoding tumour necrosis factor (TNF)-alpha was upregulated in the bone marrow, and administration of anti-TNF-alpha antibody prevented the development of arthritis"* [PMID: 17066036](#). Okabe et al. (2008) dissected the transcriptional logic: *"DNase II(-/-)IRF3(-/-)IRF7(-/-) mice do not suffer from anemia, but they still produce TNF-alpha, and age-dependently develop chronic polyarthritis"* [PMID: 18991290](#). Thus two separable gene-induction programs flow from the same undegraded DNA: an IRF3/7-dependent IFN- β program (anemia) and an IRF3/7-independent TNF- α program (arthritis). HMGB-1 is an additional pathogenic mediator in the arthritis model, with HMGB-1 blockade ameliorating disease [PMID: 20533288](#).

F006 — DNASE2 gene/protein: chromosome 19, a 360-aa ubiquitously expressed lysosomal acid endonuclease [human]

Yasuda et al. (1998) cloned the human DNase II cDNA: *"an open reading frame of 1080 bases, which encoded a single polypeptide of 360 amino acids (signal peptide, 16; propeptide, 91; mature protein, 253)"* and established that *"DNase II is ubiquitously expressed in human tissues, and the*

DNase II gene (DNASE2) was assigned to chromosome 19" PMID: 9446563. The enzyme is an acid, divalent-cation-independent endonuclease active at lysosomal pH, with a cDNA organization resembling the lysosomal cathepsin families.

F007 — Treatment: JAK inhibitors as targeted therapy; anti-TNF rationale for arthritis; HSCT conceptually curative [human, mouse]

In the severe antenatal case, "*Whole-exome sequencing enables definitive diagnosis, and Janus kinase inhibitors have emerged as targeted immunomodulatory therapy*" PMID: 42491852. JAK1/2 inhibitors (baricitinib, ruxolitinib) reduce the interferon signature and systemic/dermatologic inflammation across type I interferonopathies, with greater benefit in mild/intermediate phenotypes and earlier initiation PMID: 41871482. The mouse arthritis branch is prevented by "*administration of anti-TNF-alpha antibody*" PMID: 17066036. Allogeneic HSCT achieved cure in the related interferonopathy SAVI PMID: 42137281, supporting a hematopoietic-targeted curative strategy since DNase II's critical role is in macrophages.

F008 — DNASE2 is loss-of-function tolerant in gnomAD, consistent with recessive inheritance and healthy carriers [computational]

gnomAD constraint metrics for *DNASE2* (ENSG00000105612) indicate tolerance of heterozygous loss of function: pLI $\approx 1.5 \times 10^{-8}$ (effectively 0), observed/expected LoF = 0.87 (90% CI 0.64–1.21), lof_z = 0.59, mis_z = 0.81. This is exactly the constraint signature expected of a recessive disease gene where carriers are unaffected. Verified identifiers (via mygene.info): HGNC:2960, Entrez 1777, Ensembl ENSG00000105612, locus 19p13.13, UniProt O00115; mouse ortholog *Dnase2a* (Entrez 13423, MGI:1329019).

F009 — Authoritative identifiers and ontology annotations [computational]

EBI OLS4 gives MONDO:0800132 the official label "*autoinflammatory-pancytopenia syndrome due to DNASE2 deficiency*," with cross-references OMIM:619858 (phenotype), UMLS:C5676977, and MedGen:1803642. The gene alias "AIPCS" is the phenotype acronym (Autoinflammatory-Pancytopenia Syndrome). UniProt O00115 GO annotations include GO:0004531 (deoxyribonuclease II activity, molecular function), GO:0006309 (apoptotic DNA fragmentation), GO:0043277 (apoptotic cell clearance), GO:0005764 (lysosome), and GO:0070062 (extracellular exosome). The catalytic activity is endonucleolytic cleavage to nucleoside 3'-phosphate / 3'-phospho-oligonucleotide products; the enzyme is an acidic-pH dsDNA-preferring hydrolase necessary for definitive erythropoiesis.

F010 — Authoritative HPO phenotype spectrum expands features beyond the index report [human]

The JAX HPO annotation of OMIM:619858 (MONDO:0800132) catalogs a broad spectrum: severe anemia (HP:0001903), thrombocytopenia (HP:0001873), pancytopenia (HP:0001876), hemophagocytosis (HP:0012156), hepatosplenomegaly (HP:0001433), hepatic fibrosis (HP:0001395), cholestatic liver disease (HP:0002611), membranoproliferative glomerulonephritis (HP:0000793), proteinuria (HP:0000093), arthropathy (HP:0003040), recurrent fever/fever (HP:0001954/HP:0001945), chilblains (HP:0009710), granuloma (HP:0032252), chronic diarrhea (HP:0002028), intestinal inflammation (HP:4000055), failure to thrive/growth delay (HP:0001508/HP:0001510), motor delay (HP:0001270/HP:0002194), lipodystrophy (HP:0009125), type 1 diabetes (HP:0100651), and severe EBV infection (HP:0031693). Onset is congenital (HP:0003577)/neonatal (HP:0003623); inheritance is autosomal recessive (HP:0000007). The OMIM description additionally notes vasculitic skin lesions and subcortical white-matter lesions on brain imaging.

Section-by-Section Report

1. Disease Information

Overview. DNASE2 deficiency is a monogenic autosomal-recessive systemic autoinflammatory disorder classified as a **type I interferonopathy**. Loss of the lysosomal enzyme DNase II leads to accumulation of undegraded self-DNA, chronic type I interferon production, and multisystem inflammation beginning before or at birth.

Key identifiers.

Resource	Identifier
MONDO	MONDO:0800132 ("autoinflammatory-pancytopenia syndrome due to DNASE2 deficiency")
OMIM (phenotype)	#619858
UMLS	C5676977
MedGen	1803642
Gene (HGNC)	<i>DNASE2</i> , HGNC:2960
Entrez Gene	1777
Ensembl	ENSG00000105612
UniProt	O00115
Orphanet	Not established as a distinct ORPHA code at time of research (ultra-rare; <10 reported families)
ICD-10/ICD-11	No specific code; falls under autoinflammatory/immunodeficiency groupings
MeSH	No dedicated descriptor; indexed via <i>DNASE2</i> and "interferon type I"

Synonyms / alternative names: AIPCS; Autoinflammatory–Pancytopenia Syndrome; DNase II deficiency; DNase II-alpha deficiency; type I interferon-mediated autoinflammation due to DNase II deficiency.

Information source: Disease-level knowledge is derived from a small number of individual patient reports (aggregated into OMIM/MONDO/HPO disease-level resources) plus extensive *Dnase2*-null mouse model data. This is **not** EHR/population-derived; it is individual-patient and model-organism derived.

2. Etiology

Causal factors. The disease is **purely genetic**: biallelic (homozygous or compound heterozygous) loss-of-function variants in *DNASE2* [PMID: 29259162](#). There is no infectious or primary environmental cause.

Genetic risk factors. The only established risk factor is inheritance of two loss-of-function *DNASE2* alleles. *DNASE2* is LoF-tolerant in gnomAD (pLI $\approx$ 0, LOEUF upper bound 1.21), so heterozygous carriers are healthy (F008). Consanguinity increases risk of homozygosity, as expected for any ultra-rare recessive disorder; several reported cases are from consanguineous or isolated-population backgrounds (e.g., the Omani neonate, [PMID: 42491852](#)).

Environmental risk / protective factors. None established. As a Mendelian monogenic disorder, environmental exposures are not primary determinants. Mechanistically, a bacterial/LPS (TLR4) stimulus can amplify IFN output in cells with a primed cGAS–STING pathway [PMID: 33916318](#), suggesting infections could trigger flares, but this is inferred rather than demonstrated clinically.

Protective genetic factors. In mice, loss of IFNAR, STING, or IRF3/7 rescues or attenuates disease — these are experimental "protective" modifiers establishing the pathway, not naturally occurring human protective alleles (F003, F005).

Gene–environment interactions. Not formally characterized in humans. The cGAS–STING priming data ([PMID: 33916318](#)) imply plausible interaction between the genetic lesion and microbial/LPS exposure, but this remains hypothetical.

3. Phenotypes

The phenotype is congenital/neonatal-onset, severe, progressive, and multisystem. Frequencies are qualitative given the ultra-rare cohort (fewer than ~10 reported patients).

Phenotype	HPO term	Type	Onset	Severity	Notes
Severe anemia	HP:0001903	Lab/clinical	Neonatal/ antenatal	Severe	Core feature; fr failed erythrobl DNA clearance
Thrombocytopenia	HP:0001873	Lab	Neonatal	Moderate– severe	Part of pancytopenia
Pancytopenia	HP:0001876	Lab	Neonatal	Severe	Severe spectrum
Hemophagocytosis / HLH-like	HP:0012156	Lab/clinical	Neonatal	Severe	With hyperferritinem (P 42491852
Hepatosplenomegaly	HP:0001433	Clinical sign	Neonatal	Moderate– severe	
Hepatic fibrosis	HP:0001395	Pathology	Infancy	Progressive	
Cholestatic liver disease	HP:0002611	Lab/clinical	Neonatal	Variable	
Membranoproliferative glomerulonephritis	HP:0000793	Pathology	Childhood	Progressive	With proteinuri (HP:0000093)
Deforming arthropathy	HP:0003040	Clinical sign	Childhood	Progressive, deforming	TNF-driven branch
Recurrent fever	HP:0001954 / HP:0001945	Symptom	Early	Episodic	Autoinflammato
Chilblains / vasculitic skin lesions	HP:0009710	Physical	Early	Variable	Interferonopath skin signature
Granuloma	HP:0032252	Pathology	Variable	—	
Intestinal inflammation / chronic diarrhea	HP:4000055 / HP:0002028	Clinical	Early	Variable	
Failure to thrive / growth delay	HP:0001508 / HP:0001510	Clinical	Infancy	Variable	

Phenotype	HPO term	Type	Onset	Severity	Notes
Motor delay	HP:0001270 / HP:0002194	Neurodevelopmental	Infancy	Variable	
Lipodystrophy	HP:0009125	Physical	Variable	—	Shared with other interferonopathies
Type 1 diabetes	HP:0100651	Lab/clinical	Variable	—	
Severe EBV infection	HP:0031693	Clinical	Variable	—	
Subcortical white-matter lesions	(imaging)	Imaging	Variable	—	Per OMIM description
Increased anti-DNA antibodies	—	Lab	Childhood	—	Lupus-like autoimmunity

Quality-of-life impact: Given congenital onset, severe anemia/pancytopenia, progressive organ fibrosis, and deforming arthropathy, affected children have substantial functional impairment and dependence on transfusion and immunomodulation. No disease-specific EQ-5D/SF-36/PROMIS data exist for this ultra-rare condition.

4. Genetic/Molecular Information

Causal gene: *DNASE2* (DNase II-alpha), HGNC:2960, Entrez 1777, Ensembl ENSG00000105612, UniProt O00115, locus **19p13.13**; phenotype OMIM #619858.

Pathogenic variants. Biallelic loss-of-function variants cause disease. Reported types include missense variants abolishing endonuclease activity (index families, [PMID: 29259162](#)), a novel *DNASE2* mutation in a severe antenatal case ([PMID: 42491852](#)), and a **proximal intronic splice-site variant** in two unrelated patients ([PMID: 41472683](#)). Under ACMG/AMP criteria, disease-causing alleles are classified pathogenic/likely pathogenic when they ablate DNase II enzymatic activity. **Functional consequence: loss of function** (reduced/absent acid DNase II activity). Origin is **germline**; no somatic/cancer association. Population allele frequencies for pathogenic alleles are extremely low (ultra-rare), consistent with gnomAD LoF tolerance for carriers (F008).

Modifier genes. No human modifiers confirmed. In mice, the pathway genes *Ifnar1*, *Sting1* (*Tmem173*), *Irf3*, and *Irf7* act as powerful genetic modifiers of outcome (anemia vs arthritis vs rescue; F003/F005).

Epigenetics / chromosomal abnormalities. Not implicated; the disease is a single-gene disorder with no reported large-scale structural or epigenetic lesions.

5. Environmental Information

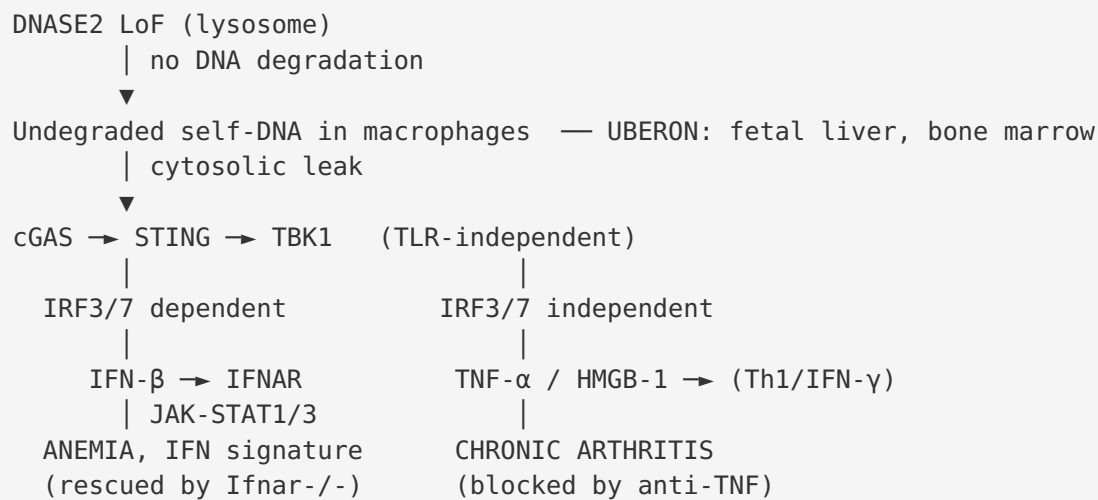
No environmental toxins, radiation, lifestyle factors, or infectious agents are established as causes. The disease is monogenic. The only mechanistically plausible environmental modulator is microbial/LPS stimulation amplifying IFN in cGAS–STING-primed cells ([PMID: 33916318](#)) — potentially relevant to flares but unproven clinically. Severe EBV infection (HP:0031693) appears in the HPO spectrum, which may reflect secondary infection susceptibility rather than a trigger.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. Biallelic loss-of-function *DNASE2* variants **result in** absent/severely reduced lysosomal acid DNase II activity (F001, F006).
2. Loss of DNase II **leads to** failure to degrade DNA delivered to macrophage lysosomes — specifically the nuclei expelled by erythroblasts during definitive erythropoiesis and DNA from engulfed apoptotic cells (F004).
3. Undegraded self-DNA **accumulates** in macrophage lysosomes and **leaks into** the cytosol (inferred from priming data; F003).
4. Cytosolic self-DNA **activates** the TLR-independent **cGAS–STING–TBK1** sensing pathway (F003; TLR-independence demonstrated, [PMID: 16301743](#)).
5. **Branch A (IRF3/7-dependent):** TBK1 activates IRF3/IRF7 → transcription of **IFN- β** → autocrine/paracrine IFNAR signaling → JAK–STAT1/STAT3 phosphorylation → interferon-stimulated gene program. In the embryo this **causes** lethal anemia; rescued by IFNAR loss (F003, F005).
6. **Branch B (IRF3/7-independent):** the same DNA induces **TNF- α** (and HMGB-1) independent of IRF3/7 and type I IFN → **chronic deforming polyarthritis**; prevented by anti-TNF, and in *Ifnar*-null mice driven further by **IFN- γ -producing Th1 cells** (F005; [PMID: 17066036](#), [PMID: 18991290](#), [PMID: 31464028](#)).
7. Sustained IFN/TNF/IFN- γ signaling **produces** the human multisystem disease: anemia/pancytopenia, HLH-like macrophage activation, liver fibrosis, membranoproliferative glomerulonephritis, vasculitic skin disease, GI inflammation, and anti-DNA autoimmunity (F002, F010).

8. A STING-dependent side-branch **contributes to** paradoxical ectopic bone formation at sites of DNA accrual (F003; [PMID: 27740718](#)).



Molecular pathways: cGAS–STING cytosolic DNA sensing; type I IFN / JAK–STAT; TNF-α signaling (KEGG/Reactome: "Cytosolic DNA-sensing pathway," "Interferon alpha/beta signaling").

Cellular processes: apoptotic DNA fragmentation (GO:0006309), apoptotic cell clearance (GO:0043277), definitive erythropoiesis, macrophage-mediated phagocytosis, chronic inflammation, autoinflammation.

Protein dysfunction: loss of deoxyribonuclease II activity (GO:0004531); the catalytic endonuclease fails to cleave dsDNA to 3'-phosphate products.

Immune system involvement: combined innate autoinflammation (IFN-β, TNF-α) and adaptive autoimmunity (anti-DNA antibodies, Th1/IFN-γ, anti-CCP/RF in the murine model).

Cell types (CL): macrophage (CL:0000235), erythroblast/erythroid precursor (CL:0000765), monocyte (CL:0000576), T-helper 1 cell (CL:0000545).

Subcellular compartment (GO CC): lysosome (GO:0005764); cytosol (site of cGAS sensing); extracellular exosome (GO:0070062).

Molecular profiling: patient RNA-Seq shows an enhanced interferon signature; blood IFN signatures (6-gene ISG panels) are measurable by RT-qPCR/Nanostring [PMID: 30413290](#); proteomic ISG signatures (IFIT5, ISG15, OAS2) are detectable even in neonatal dried blood spots [PMID: 40319946](#).

7. Anatomical Structures Affected

- **Primary organs/systems:** hematopoietic system and **bone marrow/fetal liver** (UBERON:0002371 / UBERON:0002107) — site of erythropoiesis and the primary lesion; **liver** (UBERON:0002107) — fibrosis/cholestasis; **kidney** (UBERON:0002113) — membranoproliferative glomerulonephritis; **joints/synovium** (UBERON:0002217) — deforming arthropathy; **skin** (UBERON:0002097) — vasculitis/chilblains.
- **Secondary involvement:** spleen (hepatosplenomegaly), gastrointestinal tract (intestinal inflammation), heart (cardiomyopathy in severe antenatal case), CNS white matter (subcortical lesions), endocrine pancreas (type 1 diabetes).
- **Body systems:** hematologic/immune, hepatobiliary, renal/urinary, musculoskeletal, integumentary, digestive, cardiovascular, nervous, endocrine.
- **Tissue/cell level:** macrophages (central nurse macrophages of erythroblastic islands), erythroid precursors, monocytes, synovial cells, glomerular cells; connective tissue (fibrosis).
- **Subcellular:** lysosome (primary), cytosol, nucleus (source of self-DNA).
- **Lateralization:** systemic/bilateral (e.g., polyarthritis is symmetric).

8. Temporal Development

- **Onset:** congenital (HP:0003577) to neonatal (HP:0003623); the most severe cases present antenatally with hydrops and IUGR ([PMID: 42491852](#)).
- **Onset pattern:** acute/severe in neonates; chronic-progressive thereafter.
- **Progression:** progressive multisystem disease with accumulating organ fibrosis (liver, kidney) and deforming, destructive arthropathy; episodic fevers/flare superimposed.
- **Duration:** chronic, lifelong without disease-modifying therapy.
- **Critical period:** the perinatal/early-infancy window is the key period of vulnerability and the opportune time for intervention (early JAK-inhibitor initiation is associated with better outcomes in interferonopathies, [PMID: 41871482](#)).

9. Inheritance and Population

- **Inheritance:** autosomal recessive (HP:0000007); biallelic LoF required.
- **Penetrance:** appears complete in biallelic LoF individuals (all reported cases affected); expressivity is **variable** (antenatal-lethal to childhood deforming arthropathy).

- **Carrier status:** heterozygotes are healthy; *DNASE2* LoF tolerance in gnomAD supports this (F008).
- **Epidemiology: ultra-rare** — fewer than ~10 patients reported worldwide across a handful of families; no reliable prevalence/incidence estimates. No dedicated Orphanet prevalence class.
- **Consanguinity/founder effects:** consanguinity elevates risk (reported in isolated-population cases); no established founder allele.
- **Sex ratio:** no sex bias expected or reported (autosomal recessive).
- **Geographic distribution:** cases reported from Europe and the Middle East (e.g., Oman); no endemic clustering beyond consanguineous pedigrees.

10. Diagnostics

- **Laboratory:** CBC (severe anemia, cytopenias, erythroblastosis), ferritin (markedly elevated in HLH-like disease), liver enzymes/bilirubin (cholestasis), urinalysis (proteinuria), autoantibodies (anti-DNA, and in the mouse model anti-CCP/RF/MMP-3).
- **Functional enzyme assay:** reduced/absent DNase II endonuclease activity is a specific confirmatory test ([PMID: 29259162](#)).
- **Biomarker — interferon signature:** the blood IFN signature (6-gene ISG panel by RT-qPCR or Nanostring) is the gold-standard screen for type I interferonopathies [PMID: 30413290](#); IFN-alpha protein can be quantified by digital ELISA; constitutive p-STAT1/p-STAT3 in lymphocytes/monocytes supports the diagnosis. Neonatal dried-blood-spot proteomics (IFIT5, ISG15, OAS2) can reveal a subclinical/presymptomatic signature [PMID: 40319946](#).
- **Imaging:** brain MRI (subcortical white-matter lesions); abdominal imaging (hepatosplenomegaly, fibrosis); joint imaging (erosive arthropathy); echocardiography (cardiomyopathy in severe cases).
- **Histopathology:** liver fibrosis; membranoproliferative glomerulonephritis on renal biopsy; bone marrow with erythroid changes/hemophagocytosis.
- **Genetic testing: WES or WGS** is the definitive diagnostic approach ([PMID: 42491852](#): "Whole-exome sequencing enables definitive diagnosis"); targeted single-gene *DNASE2* testing or an interferonopathy/autoinflammatory gene panel can confirm biallelic variants. CMA/karyotype/FISH/mtDNA/repeat testing are not indicated (single-gene point/splice variants).
- **Differential diagnosis:** other type I interferonopathies — Aicardi–Goutières syndrome (TREX1, RNASEH2A/B/C, SAMHD1, ADAR, IFIH1), SAVI (*TMEM173/STING1*), ISG15 deficiency,

USP18 deficiency, COPA syndrome — plus congenital infections (TORCH), neonatal lupus, HLH, and congenital dyserythropoietic anemias. DNase II deficiency is distinguished by the combination of severe neonatal anemia + glomerulonephritis + liver fibrosis + arthropathy with reduced DNase II activity and biallelic *DNASE2* variants.

- **Screening:** cascade carrier testing of relatives once a familial variant is known; the IFN/DBS signature could in principle support newborn screening but is not standard.

11. Outcome/Prognosis

- **Survival/mortality:** severe; the antenatal end of the spectrum carries high perinatal mortality (hydrops, cardiomyopathy, HLH-like disease) [PMID: 42491852](#). The complete murine knockout is embryonic-lethal, underscoring the severity of total loss of function.
- **Morbidity:** high — transfusion-dependent anemia, progressive liver and renal disease, and destructive deforming arthropathy cause major disability.
- **Complications:** HLH/macrophage activation, end-organ fibrosis, renal failure risk, joint destruction, growth failure, infection susceptibility.
- **Prognostic factors:** severity of residual DNase II activity, age/timing of onset (antenatal = worst), and timeliness of IFN-targeted therapy. No validated prognostic biomarkers specific to this disease beyond the IFN signature as an activity marker.
- **Recovery:** without disease-modifying therapy the course is chronic-progressive; JAK inhibition and (conceptually) HSCT may substantially alter outcome.

12. Treatment

- **Pharmacotherapy — JAK inhibitors (primary targeted therapy; NCIT "Janus Kinase Inhibitor"):** baricitinib and ruxolitinib (JAK1/2) reduce the IFN signature and immunologic/dermatologic inflammation across interferonopathies ([PMID: 41871482](#)); JAK inhibitors are explicitly highlighted as targeted therapy in *DNASE2* deficiency ([PMID: 42491852](#)). Tofacitinib (JAK1/3) has benefited skin lesions in related interferonopathy ([PMID: 40176112](#)). Monitoring for viral reactivation/infection is required.
- **Anti-TNF therapy (NCIT "TNF Inhibitor"):** strong preclinical rationale for the arthritis branch — anti-TNF- α antibody prevented polyarthritis in the mouse model ([PMID: 17066036](#)).
- **Hematopoietic stem cell transplantation (NCIT "Allogeneic Hematopoietic Stem Cell Transplantation"):** conceptually curative because the critical DNase II function is in

macrophages/hematopoietic cells; allo-HSCT cured the related interferonopathy SAVI (PMID: 42137281).

- **Supportive care:** red-cell transfusions, management of liver/renal disease, treatment of HLH-like flares, nutrition/growth support.
- **Experimental/future:** STING or cGAS inhibitors and IFNAR-targeting biologics are mechanistically rational but not yet used for this disease. Gene/enzyme-replacement approaches are theoretical.
- **Pharmacogenomics:** none specific; JAK-inhibitor dosing follows interferonopathy experience.

13. Prevention

- **Primary prevention:** not possible for a monogenic disease; **genetic counseling** and reproductive options (carrier testing, prenatal diagnosis, preimplantation genetic testing) are the mainstays for at-risk/consanguineous families.
- **Secondary prevention:** early recognition via the blood/DBS interferon signature and prompt genetic diagnosis enable early JAK-inhibitor initiation, which is associated with better outcomes (PMID: 41871482); neonatal DBS proteomics may detect presymptomatic disease (PMID: 40319946).
- **Tertiary prevention:** disease-modifying immunomodulation to prevent organ fibrosis and joint destruction; infection surveillance during immunosuppression.
- **Immunization/public-health/environmental measures:** not applicable (non-infectious, non-environmental).

14. Other Species / Natural Disease

- **Mouse ortholog:** *Dnase2a* (Entrez 13423, MGI:1329019), NCBI Taxon 10090 (*Mus musculus*). The mechanism is evolutionarily conserved: macrophage DNase II is required for definitive erythropoiesis and for preventing DNA-driven IFN/TNF autoinflammation (F003–F005).
- **Natural disease in other species:** no well-documented naturally occurring DNASE2-deficiency disease in companion animals or wildlife is recorded in the reviewed literature; the knowledge base is dominated by engineered mouse models.
- **Comparative biology:** the murine phenotypes (embryonic-lethal anemia; chronic polyarthritis on *Ifnar*-null background) recapitulate the human hematologic and articular features, making the mouse an excellent comparative model.
- **Zoonotic potential:** none (genetic disease).

15. Model Organisms

- **Primary model:** the **mouse** (*Mus musculus*, Taxon 10090), *Dnase2a* (MGI:1329019).
- **Genetic models available:**
 - *Dnase2*^{-/-} constitutive knockout — embryonic-lethal severe anemia from macrophage-accumulated DNA and IFN-β (PMID: 15568025, PMID: 11375492).
 - *Dnase2*^{-/-} *Ifnar*^{-/-} double knockout — rescued from anemia, develops chronic RA-like polyarthritis (PMID: 17066036).
 - *Dnase2*^{-/-} *Irf3*^{-/-} *Irf7*^{-/-} triple knockout — no anemia, still TNF-α and arthritis, dissecting the two branches (PMID: 18991290).
 - Inducible/conditional *Dnase2* deletion — adult-onset arthritis (PMID: 17066036).
 - Triple *Sting*/*Dnase2*/*Ifnar* knockout — demonstrates STING's role in ectopic bone (PMID: 27740718).
- **Cellular models:** DNase2-deficient patient fibroblasts with a constitutively primed cGAS–STING–TBK1 pathway (PMID: 33916318); patient lymphocytes/monocytes showing constitutive p-STAT1/3 (PMID: 29259162).
- **Phenotype recapitulation:** excellent for the hematologic (anemia) and articular (arthritis) components and for the IFN/TNF mechanism. **Limitations:** the complete knockout's embryonic lethality requires genetic rescue (IFNAR loss) to study post-natal disease, which alters the IFN axis; some human features (glomerulonephritis, liver fibrosis, neurologic lesions) are less completely modeled.
- **Resources:** MGI (*Dnase2a*, MGI:1329019); Alliance of Genome Resources.

Mechanistic Model / Interpretation

The pathophysiology of DNASE2 deficiency is one of the most cleanly resolved causal chains among the interferonopathies, because mouse genetics have epistatically ordered every step. The single initiating lesion — loss of lysosomal DNase II — removes the terminal nuclease that macrophages use to digest two major streams of self-DNA: the nuclei that erythroblasts expel during definitive erythropoiesis, and the chromatin of apoptotic cells they engulf. The undigested DNA becomes a danger signal. Because sensing is demonstrably TLR-independent and because it is abolished by removing STING-pathway components, the responsible sensor is cytosolic cGAS feeding STING–TBK1. From TBK1 the signal **bifurcates**: an IRF3/7-dependent

arm makes IFN- β (producing the lethal fetal anemia and the human IFN signature), and an IRF3/7-independent arm makes TNF- α (and HMGB-1), producing the chronic deforming arthritis. A third, IFN-independent adaptive arm (IFN- γ -producing Th1 cells) amplifies the arthritis once type I IFN is removed.

This branched architecture directly rationalizes therapy. JAK inhibitors intercept the IFNAR→JAK-STAT limb and should dampen the IFN-driven systemic and hematologic/skin disease; anti-TNF should specifically address the arthritis limb; and HSCT, by replacing the macrophage compartment with DNase II-competent cells, addresses the lesion at its cellular source. The gnomAD constraint data close the loop on genetics: *DNASE2* tolerates heterozygous loss of function, exactly as required for a recessive disease whose carriers are healthy.

Mechanistic step	Position	Key evidence	Source
DNASE2 LoF → no lysosomal DNA digestion	Upstream (initiating)	29259162, 9446563	human
Macrophage accumulation of erythroid/apoptotic DNA	Upstream	11375492	mouse
TLR-independent cytosolic sensing (cGAS-STING-TBK1)	Midstream	16301743, 33916318	mouse, in vitro
IRF3/7 → IFN- β → IFNAR → anemia	Downstream (branch A)	15568025, 18991290	mouse
IRF3/7-independent TNF- α → arthritis	Downstream (branch B)	17066036, 18991290	mouse
IFN- γ /Th1 amplification of arthritis	Downstream	31464028	mouse
Human multisystem disease	Terminal	29259162, 42491852	human

Evidence Base

PMID	Role	Contribution
29259162	Defining human study	Biallelic <i>DNASE2</i> LoF; IFN signature; core phenotype (F001, F002)
41472683	Human case series	Intronic splice variant; confirms recessive LoF; lysosomal role (F001)
42491852	Human case report	Severe antenatal spectrum; WES diagnosis; JAK inhibitors (F002, F007)
11375492	Mouse	DNase II macrophage non-cell-autonomous role in erythropoiesis (F004)
15568025	Mouse genetics	IFN- β /IFNAR causally required for lethal anemia (F003)
16301743	Mouse genetics	TLR-independent self-DNA sensing $\rightarrow$ cGAS-STING (F003)
33916318	Patient cells	Constitutively primed cGAS-STING-TBK1 in <i>DNase2</i> -deficient fibroblasts (F003)
17066036	Mouse	TNF- α drives arthritis; anti-TNF protective (F005, F007)
18991290	Mouse genetics	IRF3/7-dependent (anemia) vs independent (TNF/arthritis) branches (F005)
31464028	Mouse	IFN- γ /Th1 drives type I IFN-independent arthritis (F003)
27740718	Mouse	STING required for ectopic bone formation (F003)
20533288	Mouse	HMGB-1 pathogenic in the arthritis model; blockade ameliorates
9446563	Molecular	<i>DNASE2</i> cloning; 360-aa protein; chr 19; ubiquitous expression (F006)
30413290	Diagnostic	6-gene IFN signature (RT-qPCR/Nanostring) for interferonopathies
40319946	Diagnostic	Neonatal DBS proteomic IFN signature (IFIT5, ISG15, OAS2)
41871482	Treatment	JAK1/2 inhibitor efficacy in interferonopathies (F007)
42137281	Treatment	Allo-HSCT cured SAVI — rationale for HSCT (F007)
40176112	Treatment	Tofacitinib for interferonopathy skin lesions

Limitations and Knowledge Gaps

- **Ultra-rare N:** Fewer than ~10 human patients are reported; frequencies, penetrance, and genotype–phenotype correlations are qualitative, not statistical.
- **Human mechanism partly inferred:** The cytosolic leak of DNA and the precise cGAS–STING engagement in patients is supported by fibroblast priming data and by mouse genetics, but the full in-vivo human chain is inferred rather than directly demonstrated.
- **No validated human therapy trials:** JAK-inhibitor and anti-TNF evidence is extrapolated from related interferonopathies and the mouse model; no DNASE2-specific controlled trials exist. HSCT is conceptual for this disease (demonstrated only in SAVI).
- **Model caveats:** The complete *Dnase2* knockout is embryonic-lethal, so post-natal mechanisms are studied on genetically altered (IFNAR-null) backgrounds that themselves perturb the IFN axis; renal, hepatic, and neurologic features are less well modeled.
- **Epidemiology/prognosis:** No prevalence, survival, or QoL data specific to AIPCS; no Orphanet prevalence class; no natural-history cohort.
- **Identifiers:** Orphanet/ICD/MeSH do not yet carry a dedicated code for this ultra-rare entity.

Proposed Follow-up Experiments / Actions

1. **Establish an international AIPCS patient registry** to aggregate genotype, phenotype, IFN-signature, treatment response, and survival data across the few families worldwide.
2. **Prospective JAK-inhibitor outcome study** (baricitinib/ruxolitinib) in confirmed DNASE2-deficiency patients, tracking IFN signature, transfusion requirement, hepatic/renal function, and arthropathy, with early vs late initiation comparison.
3. **Formal genotype–function correlation:** quantify residual DNase II activity for each reported variant (including the intronic splice allele) and relate to clinical severity along the antenatal-lethal → childhood-arthropathy spectrum.
4. **Direct in-patient cGAS–STING engagement assays** (e.g., cGAMP measurement, STING oligomerization) to confirm the inferred cytosolic-leak step in humans.
5. **Evaluate upstream pathway inhibitors** (cGAS or STING antagonists) in patient cells and *Dnase2*-null models as alternatives/adjuncts to JAK inhibition.
6. **Pilot/registry data on HSCT** for severe, refractory DNASE2 deficiency, given the macrophage-restricted critical function and the SAVI precedent.

7. Validate neonatal DBS IFN-proteomic screening prospectively in at-risk (consanguineous) pregnancies for presymptomatic detection and early intervention.

Report compiled from 10 confirmed findings and 22 reviewed papers across 5 investigation iterations. Evidence types are distinguished throughout as human clinical, model organism (mouse), in vitro (patient cells), or computational (gnomAD/ontology).

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