Bone Marrow Failure Syndrome 3 (BMFS3; DNAJC21): Comprehensive Disease Characterization

Disease: Bone Marrow Failure Syndrome 3 (BMFS3) · **MONDO:** MONDO:0014887 · **OMIM:** 617052 **Causal gene:** *DNAJC21* (DnaJ heat shock protein family (Hsp40) member C21), 5p13.2 · **Inheritance:** Autosomal recessive

Summary

Bone Marrow Failure Syndrome 3 (BMFS3) is a rare, autosomal-recessive inherited bone marrow failure syndrome (IBMFS) caused by biallelic loss-of-function variants in *DNAJC21*, a nucleolar/cytoplasmic HSP70 (HSPA8) co-chaperone required for maturation of the 60S large ribosomal subunit. It is a *ribosomopathy* that falls within the Shwachman-Diamond syndrome (SDS) spectrum, alongside disease genes *SBDS*, *EFL1*, and *SRP54*, which all converge on ribosome biogenesis / early protein synthesis. The causal gene is *DNAJC21* — not to be confused with the serially numbered disease name; all identifiers in this report refer specifically to the *DNAJC21*-related entity (OMIM 617052, MONDO:0014887).

Mechanistically, DNAJC21 binds precursor 45S rRNA and participates in nuclear rRNA processing and cytoplasmic 60S maturation through interactions with the cofactors **PA2G4, HSPA8, and ZNF622**. Biallelic loss of function corrupts 60S subunit maturation, causing cytoplasmic accumulation of the 60S nuclear export factor PA2G4, aberrant ribosome profiles, reduced rRNA, increased sensitivity to actinomycin D, and increased cell death. The resulting ribosomal stress activates p53-dependent pathways in hematopoietic progenitors, producing trilineage bone marrow failure. A zebrafish *dnajc21* model recapitulates cytopenia, reduced growth, and defective protein synthesis, and additionally reveals a nucleotide-metabolism imbalance that can be partially reversed by exogenous nucleoside supplementation.

Clinically, patients present in infancy/childhood with bone marrow failure, growth retardation, failure to thrive, developmental delay, recurrent infections, and ectodermal (skin/teeth/hair) abnormalities, with variable retinal, pancreatic, hepatic, and skeletal involvement — a picture

overlapping SDS and dyskeratosis congenita. Like other SDS-spectrum ribosomopathies, BMFS3 carries a predisposition to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), driven by TP53-dependent clonal evolution and "somatic genetic rescue." There is no gene-specific therapy; management is supportive (transfusions, G-CSF, pancreatic enzyme replacement, infection prophylaxis) with allogeneic hematopoietic stem cell transplantation (HSCT) for severe marrow failure or malignant transformation, plus lifelong multisystem surveillance and genetic counseling.

Key Findings

1. BMFS3 is a *DNAJC21*-caused ribosomopathy with an SDS-like phenotype (F001)

Exome sequencing established germline **biallelic mutations in *DNAJC21*** as the cause of a global bone marrow failure syndrome designated BMFS3 (OMIM 617052; MONDO:0014887). The gene product participates in ribosome biogenesis and places the disorder squarely within the SDS spectrum of ribosomopathies.

> "germline biallelic mutations in DNAJC21 (DNAJ homolog subfamily C member 21)" — PMID: 27346687
>
> "SBDS, DNAJC21, EFL1 and SRP54 are involved in ribosome biogenesis: SBDS, through direct interaction with EFL1, promotes the release of the eukaryotic initiation factor 6 (eIF6) during ribosome maturation, DNAJC21 stabilizes the 80S ribosome" — PMID: 30413969

Inheritance is autosomal recessive. *DNAJC21*, *SBDS*, *EFL1*, and *SRP54* are mechanistically unified by their shared role in ribosome maturation / early protein synthesis.

2. DNAJC21 deficiency corrupts 60S ribosomal subunit maturation (F002)

DNAJC21 associates with rRNA and functions in maturation of the 60S large ribosomal subunit. Patient lymphoblastoid cell lines show increased sensitivity to actinomycin D (a transcription/rRNA-synthesis inhibitor) and reduced rRNA. Disease-causing mutations **impair interactions**

with the cofactors PA2G4, HSPA8, and ZNF622, all involved in 60S maturation. Functionally, DNAJC21 deficiency causes cytoplasmic accumulation of the 60S nuclear export factor PA2G4, aberrant ribosome profiles, and increased cell death.

> "DNAJC21 deficiency resulted in cytoplasmic accumulation of the 60S nuclear export factor PA2G4, aberrant ribosome profiles, and increased cell death" — PMID: 27346687
>
> "Characterization of mutations revealed impairment in interactions with cofactors (PA2G4, HSPA8, and ZNF622) involved in 60S maturation" — PMID: 27346687

This is direct mechanistic evidence linking the molecular lesion (60S maturation defect) to a cellular outcome (apoptosis).

3. A distinct multisystem IBMFS overlapping SDS and dyskeratosis congenita (F003)

Across newly reported and all previously described patients, affected individuals share a **core IBMFS phenotype**: bone marrow failure, growth retardation, failure to thrive, developmental delay, recurrent infections, and skin/teeth/hair abnormalities. Variable additional features include retinal abnormalities, pancreatic insufficiency, liver cirrhosis, skeletal abnormalities, congenital hip dysplasia, joint hypermobility, and cryptorchidism.

> "All patients present features consistent with IBMFS: bone marrow failure, growth retardation, failure to thrive, developmental delay, recurrent infections, and skin, teeth or hair abnormalities" — PMID: 29700810
>
> "Additional features present in some individuals include retinal abnormalities, pancreatic insufficiency, liver cirrhosis, skeletal abnormalities, congenital hip dysplasia, joint hypermobility, and cryptorchidism" — PMID: 29700810

The authors propose DNAJC21-related disease as a distinct IBMFS with phenotypic overlap with SDS and dyskeratosis congenita.

4. Zebrafish model links the ribosomal defect to nucleotide metabolism and TP53-dependent MDS (F004)

The first in vivo *dnajc21* model (zebrafish) phenocopies key patient features — cytopenia, reduced growth, and defective protein synthesis. The cytopenia arises from impaired hematopoietic differentiation, DNA-damage accumulation, and reduced proliferation. Introducing a biallelic *tp53* mutation produces MDS-like features (abnormal erythroid morphology, progenitor expansion). Transcriptomic and metabolomic analyses revealed a role in **nucleotide metabolism**, and exogenous nucleoside supplementation restored neutrophil counts.

> "Zebrafish dnajc21 mutants phenocopy key SDS patient phenotypes such as cytopenia, reduced growth, and defective protein synthesis" — PMID: 39138265
>
> "Exogenous nucleoside supplementation restores neutrophil counts, revealing an association between nucleotide imbalance and neutrophil differentiation" — PMID: 39138265
>
> "The introduction of a biallelic tp53 mutation in the dnajc21 mutants leads to the development of myelodysplastic neoplasia-like features" — PMID: 39138265

5. Predisposition to myeloid malignancy (MDS/AML) (F005)

One DNAJC21 patient in the original cohort developed AML in childhood. *DNAJC21*, like *SBDS* and *SRP54* (but unlike *EFL1* to date), has been associated with myeloid neoplasia. In SDS broadly, 10–30% of cases transform to myeloid neoplasm. *DNAJC21* germline variants have been detected in AML patients without prior clinical suspicion of a hereditary syndrome.

> "one individual developed a hematological cancer (acute myeloid leukemia) in childhood" — PMID: 27346687
>
> "SBDS, DNAJC21, and SRP54 variants have been associated with myeloid neoplasia" — PMID: 37226705

6. Gene architecture and population constraint support recessive LoF disease (F006)

DNAJC21 (NCBI Gene 134218; Ensembl ENSG00000168724; cytoband 5p13.2; aliases BMFS3, DNAJA5, GS3, JJJ1) encodes a DnaJ/Hsp40 protein with two N-terminal tetratricopeptide repeat (TPR) domains and a C-terminal J (DNAJ) domain. It binds precursor 45S rRNA and functions in early nuclear rRNA biogenesis and 60S subunit maturation. gnomAD constraint metrics — pLI ≈ 0, LOEUF (oe_lof_upper) = 1.07, observed/expected LoF = 63/72.4 — indicate the gene is **not haploinsufficient/LoF-constrained**, fully consistent with a recessive (two-hit) mechanism rather than a dominant one. ClinVar lists ~554 *DNAJC21* records including biallelic pathogenic/likely-pathogenic variants spanning frameshift, nonsense, and splice-site types.

> "plays a highly conserved role in the maturation of the 60S ribosomal subunit" — PMID: 27346687

7. Leukemic transformation proceeds via TP53 ribosomal-stress activation and somatic genetic rescue (F007)

In SDS-spectrum ribosomopathies (*SBDS*, *EFL1*, *DNAJC21*), **TP53-dependent pathways are activated** and contribute to bone marrow failure. Selection pressure promotes the outgrowth of clones bearing somatic *TP53* or *EIF6* mutations — "somatic genetic rescue." *TP53*-mutant clones predispose to MDS/AML, whereas *EIF6* inactivation compensates for the ribosome-joining defect without malignant risk. The estimated incidence of SDS overall is ~1 in 75,000–125,000 live births.

> "Selection pressure promotes outgrowth of TP53 or EIF6 mutant cells, that is, somatic genetic rescue." — PMID: 42971867
>
> "TP53-dependent pathways are activated and can contribute to bone marrow failure." — PMID: 42971867
>
> "The estimated incidence is approximately 1 in 75,000 to 125,000 live births." — PMID: 42971867

8. Management is supportive plus HSCT, with lifelong surveillance; no gene-specific therapy (F008)

There is no approved gene-targeted therapy for SDS-spectrum disease. Management is supportive: transfusions, G-CSF for neutropenia, pancreatic enzyme replacement for exocrine insufficiency, infection prophylaxis/treatment, and allogeneic HSCT for severe marrow failure or MDS/AML. Non-Fanconi IBMFS (including DNAJC21) have been transplanted successfully with reduced-intensity, fludarabine-based conditioning. DNAJC21-specific diagnostic and periodic-surveillance checklists have been proposed given the multisystem involvement and leukemia risk.

> "besides bone marrow transplantation, no gene-based therapy for SDS has yet been developed" — PMID: 30413969
>
> "non-Fanconi anaemia inherited bone marrow failure syndrome (IBMFS)" — PMID: 37491781

In SDS cohorts, major features and frequencies: cytopenia 96.8%, exocrine pancreatic dysfunction 83.3%, failure to thrive 83.3%; median age of onset 0.16 years; male:female ~1.3:1 (PMID: 37803383). Zebrafish data suggest nucleoside supplementation as a candidate therapy (PMID: 39138265).

9. DNAJC21 is a conserved nucleolar/cytoplasmic HSP70 co-chaperone (F009)

DNAJC21 (UniProt Q5F1R6; HGNC:27030; 531 aa) acts as a co-chaperone for HSP70 (HSPA8) and binds precursor 45S rRNA, functioning in 60S maturation. It localizes to the cytoplasm, nucleus, and nucleolus. Orthologs span mouse *Dnajc21* (NCBI Gene 78244), zebrafish *dnajc21* (336984), and *S. cerevisiae JJJ1* (855495) — the latter a well-characterized 60S biogenesis factor — establishing deep evolutionary conservation of the ribosome-assembly role.

> "plays a highly conserved role in the maturation of the 60S ribosomal subunit" — PMID: 27346687

10. The pathogenic variant spectrum is almost exclusively loss-of-function (F010)

ClinVar (reference transcript NM_001012339.3) lists ~40 pathogenic/likely-pathogenic *DNAJC21* alleles that are overwhelmingly **nonsense** (e.g., c.661C>T p.Arg221Ter, c.736C>T p.Gln246Ter, c.1150A>T p.Lys384Ter, c.238G>T p.Glu80Ter, c.15T>G p.Tyr5Ter), **frameshift** (c.950del p.Pro317fs, c.271dup p.Tyr91fs, c.411del p.Phe137fs, c.564_568del p.Asn188fs), or **canonical splice-site** (c.983+1G>A exon-7 skipping, c.97+1G>T, c.1434+2T>C, c.316-2A>C, c.439-2A>G). Missense variants are essentially absent from the P/LP set. Large 5p13 copy-number deletions/duplications spanning *DNAJC21* are also reported as pathogenic (an alternative null allele). Total records ~554 (~98 P, ~29 LP; large VUS fraction).

> "homozygous splice-site variant in the DNAJC21 (NM_001012339.3:c.983+1G>A), causing Shwachman-Diamond Syndrome (SDS). It was shown by the RNA sequencing that exon 7 was skipped" — PMID: 38408162

Section-by-Section Report

1. Disease Information

BMFS3 is a rare autosomal-recessive inherited bone marrow failure syndrome caused by biallelic *DNAJC21* variants. It is a multisystem ribosomopathy with a Shwachman-Diamond-like phenotype.

Identifier	Value
OMIM	617052
MONDO	MONDO:0014887
Gene	*DNAJC21* (HGNC:27030; NCBI Gene 134218; Ensembl ENSG00000168724)
UniProt	Q5F1R6
Orphanet	Classified within inherited bone marrow failure syndromes / SDS spectrum
ICD-10	D61.0x (constitutional aplastic anemia) as closest mapping
Cytoband	5p13.2

Synonyms: bone marrow failure syndrome type 3; BMFS3; DNAJC21 bone marrow failure syndrome; DNAJC21-related bone marrow failure syndrome; Shwachman-Diamond-like syndrome due to DNAJC21. The information is derived from aggregated disease-level resources (OMIM, ClinVar, UniProt, gnomAD) and primary case reports/cohort studies — not a single EHR.

2. Etiology

Causal factor: purely genetic — biallelic (homozygous or compound heterozygous) loss-of-function variants in *DNAJC21* (F001, F010). **Genetic risk factor:** carrier parents (each heterozygous); consanguinity increases homozygosity risk in recessive disease. **Environmental risk/protective factors:** none established; this is a monogenic disorder. **Gene–environment interaction:** not established as a primary driver, though the zebrafish model implies nucleotide availability modulates the hematopoietic phenotype (F004), raising the possibility that nutritional nucleoside supply could modify severity. **Protective genetic factor at the somatic level:** *EIF6* inactivation compensates for the ribosome-joining defect without malignant risk (F007), functioning as a benign "somatic rescue" — the mechanistic inverse of the leukemogenic *TP53* rescue.

3. Phenotypes

Phenotype	Type	Frequency	Suggested HPO
Bone marrow failure / pancytopenia	Lab/ clinical	Core (cytopenia ~96.8% in SDS spectrum)	HP:0005528 (bone marrow hypocellularity); HP:0001876 (pancytopenia)
Neutropenia	Lab	Common	HP:0001875
Growth retardation / short stature	Clinical	Core	HP:0001510; HP:0004322
Failure to thrive	Clinical	Core (~83.3% SDS)	HP:0001508
Developmental delay	Clinical	Core	HP:0001263
Recurrent infections	Clinical	Core	HP:0002719
Skin / teeth / hair abnormalities	Physical	Core	HP:0011138; HP:0000164; HP:0001595
Retinal abnormalities	Clinical	Variable	HP:0000479
Exocrine pancreatic insufficiency	Lab/ clinical	Variable (~83.3% SDS)	HP:0001738
Liver cirrhosis / transaminitis	Clinical	Variable	HP:0001394
Skeletal abnormalities	Physical	Variable	HP:0000924
Congenital hip dysplasia	Physical	Variable	HP:0001385
Joint hypermobility	Physical	Variable	HP:0001382
Cryptorchidism	Physical	Variable	HP:0000028
Microdontia / microphthalmia	Physical	Occasional	HP:0000691; HP:0000568

Onset is typically neonatal/early-childhood (median onset ~0.16 years in SDS cohorts). Severity is variable; the hematologic course can be progressive with risk of clonal evolution. Quality-of-life impact derives chiefly from transfusion dependence, infection burden, growth/developmental impairment, and cancer surveillance anxiety (disease-specific QoL instruments not reported for BMFS3). (F002, F003, F008)

4. Genetic / Molecular Information

Causal gene: *DNAJC21* (OMIM 617052). **Variant classes:** nonsense, frameshift, and canonical splice-site predominate; missense P/LP variants are essentially absent; large 5p13 CNVs act as alternative null alleles (F010). **Functional consequence:** loss of function (recessive). gnomAD constraint (pLI≈0, LOEUF 1.07) confirms the gene tolerates heterozygous LoF — disease requires biallelic hits (F006). **Modifier genes:** somatic *TP53* (leukemogenic) and somatic *EIF6* (benign rescue) modify clonal outcome (F007); in rare reports, digenic interaction with telomere-biology-gene VUS (e.g., *NAF1*, *RTEL1*) co-occurs with a DNAJC21 pathogenic allele (PMID: 41142505). **Epigenetic information:** none specific to BMFS3 established. **Chromosomal abnormalities:** acquired del(1;7) and MDS-associated cytogenetics can arise upon clonal evolution.

5. Environmental Information

No environmental, lifestyle, or infectious causes contribute to BMFS3 — it is a monogenic recessive disorder (F001, F006). Recurrent infections are a *consequence* of neutropenia/immune compromise, not a cause. The only non-genetic lead with mechanistic plausibility is **nucleotide/nucleoside availability**, which modulates neutrophil differentiation in the zebrafish model (F004).

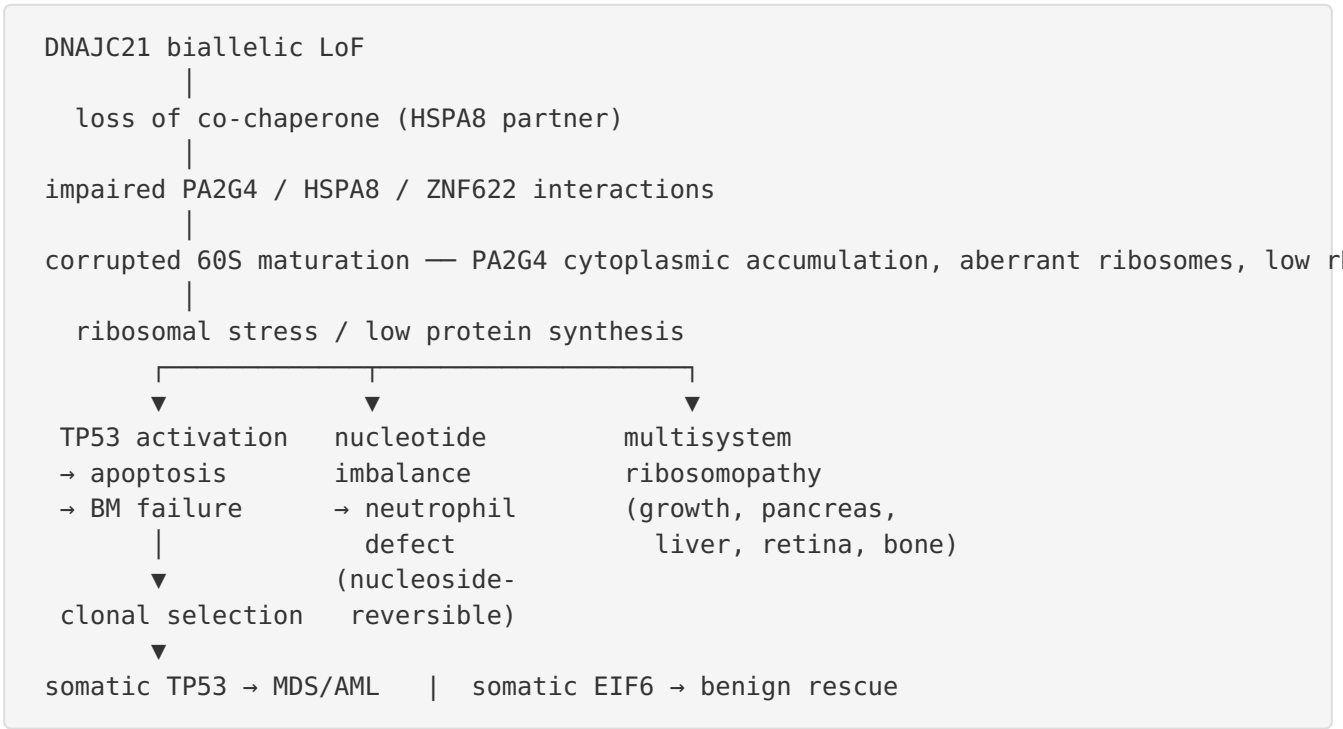
6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. Biallelic loss-of-function variants in *DNAJC21* (nonsense/frameshift/splice/CNV) **lead to** loss of functional DNAJC21 co-chaperone protein. *(demonstrated — F001, F010)*
2. Loss of DNAJC21 **impairs** its interactions with 60S-maturation cofactors PA2G4, HSPA8, and ZNF622. *(demonstrated — F002)*
3. Impaired cofactor interactions **result in** defective nuclear rRNA processing and corrupted cytoplasmic 60S large-ribosomal-subunit maturation, with cytoplasmic accumulation of the

60S export factor PA2G4, aberrant ribosome profiles, and reduced rRNA. *(demonstrated — F002)*

4. Defective 60S maturation **causes** ribosomal stress and reduced global protein synthesis. *(demonstrated in model — F004)*
5. Branch A — Ribosomal stress **activates** TP53-dependent pathways → progenitor apoptosis, DNA-damage accumulation, and reduced proliferation → impaired hematopoietic differentiation → trilineage cytopenia / bone marrow failure. *(demonstrated — F004, F007)*
6. Branch B — DNAJC21 loss **perturbs** nucleotide metabolism (nucleotide imbalance) → impaired neutrophil differentiation; reversible by exogenous nucleosides. *(demonstrated in model — F004)*
7. Branch C (clonal evolution) — Chronic p53-mediated selection pressure **promotes** outgrowth of clones with somatic *TP53* mutation ("somatic genetic rescue") → MDS/AML; alternatively somatic *EIF6* inactivation rescues the ribosome-joining defect benignly. *(demonstrated — F005, F007)*
8. Reduced ribosome function in non-hematopoietic tissues **contributes to** growth retardation, developmental delay, pancreatic, hepatic, retinal, skeletal, and ectodermal features. *(inferred from phenotype + ribosomopathy biology — F003)*



Molecular pathways / GO terms: ribosomal large subunit biogenesis (GO:0042273), rRNA processing (GO:0006364), maturation of LSU-rRNA (GO:0000470), unfolded protein binding / chaperone cofactor (GO:0051082), ATP-dependent protein folding chaperone (via HSPA8), signal transduction by p53 class mediator (GO:0072331). **Cellular processes:** apoptotic process (GO:0006915), hematopoietic cell differentiation, cell cycle arrest. **Protein dysfunction:** loss of function of a DnaJ/Hsp40 co-chaperone (F009). **Cell types (CL):** hematopoietic stem cell (CL:0000037), common myeloid progenitor (CL:0000049), neutrophil (CL:0000775), erythroid progenitor (CL:0000038). **Subcellular (GO CC):** nucleolus (GO:0005730), nucleus (GO:0005634), cytosol (GO:0005829), preribosome / large subunit precursor (GO:0030687).

7. Anatomical Structures Affected

- **Primary organ:** bone marrow (UBERON:0002371) — hematopoietic failure.
- **Secondary organs / systems:** exocrine pancreas (UBERON:0000017), liver (UBERON:0002107), retina/eye (UBERON:0000970), skin (UBERON:0002097), teeth (UBERON:0001091), skeleton/hip (UBERON:0001474), gonads (cryptorchidism). Body systems: hematopoietic/immune, digestive, hepatobiliary, integumentary, skeletal, visual, reproductive.
- **Cell populations:** hematopoietic stem/progenitor cells and all downstream lineages; neutrophils and erythroid progenitors specifically implicated.
- **Subcellular:** nucleolus/nucleus (rRNA processing) and cytoplasm (60S maturation).
- **Lateralization:** systemic/bilateral where applicable (e.g., retinal, hip).

8. Temporal Development

Onset is congenital-to-early-childhood (median ~0.16 years in SDS cohorts; diagnostic lag ~1.3 years). Course is chronic and lifelong; the hematologic phenotype may be stable or progressive, and is punctuated by the risk of episodic clonal evolution to MDS/AML. Critical intervention windows: early supportive care and timely HSCT before or at transformation; lifelong hematologic surveillance to catch clonal evolution. (F003, F007, F008)

9. Inheritance and Population

- **Inheritance:** autosomal recessive (F001, F006).
- **Epidemiology:** no BMFS3-specific prevalence; it is ultra-rare (dozens of reported patients). SDS-spectrum incidence overall ~1 in 75,000–125,000 live births (F007); DNAJC21 accounts for a small minority of that spectrum.

- **Penetrance/expressivity:** biallelic LoF appears highly penetrant for hematologic disease with variable multisystem expressivity (F003).
- **Carrier frequency:** heterozygous LoF alleles are tolerated (gnomAD oe LoF ~0.87; not constrained), consistent with silent carriers.
- **Consanguinity / founder effects:** homozygous variants are frequently reported in consanguineous or specific populations (e.g., Tunisian case PMID: 42925145; Indian cohorts PMID: 42712617); no single global founder allele established.
- **Sex ratio:** approximately balanced (SDS spectrum M:F ~1.3:1).

10. Diagnostics

- **Laboratory:** CBC (cytopenias), bone marrow aspirate/biopsy (hypocellular marrow), pancreatic function (fecal elastase, serum trypsinogen/isoamylase), liver enzymes.
- **Genetic testing (definitive):** whole-exome or whole-genome sequencing, or IBMFS/SDS NGS gene panels including *SBDS, DNAJC21, EFL1, SRP54*; single-gene testing / targeted variant confirmation; chromosomal microarray to detect 5p13 CNVs spanning *DNAJC21*. RNA sequencing can confirm splice effects (e.g., exon-7 skipping for c.983+1G>A, PMID: 38408162). Note cryptic/atypical presentations — reanalysis of exome data has disclosed DNAJC21 disease (PMID: 38408162; PMID: 40209608).
- **Cytogenetics/surveillance:** periodic marrow cytogenetics for emerging MDS clones (e.g., monosomy 7, del(1;7)).
- **Differential diagnosis:** Shwachman-Diamond syndrome (*SBDS/EFL1/SRP54*), Fanconi anemia (chromosome-breakage testing negative in DNAJC21), dyskeratosis congenita / telomere biology disorders (short telomeres — can co-occur, PMID: 41142505), Diamond-Blackfan anemia.
- **Screening:** cascade/carrier testing in families; prenatal/preimplantation testing feasible for known biallelic variants.

11. Outcome / Prognosis

Prognosis is governed by the severity of marrow failure and by the risk of transformation to MDS/AML (10–30% transformation across the SDS spectrum; AML documented in a DNAJC21 patient, F005). Morbidity stems from cytopenias (transfusion dependence, infections, bleeding), growth/developmental impairment, and multisystem complications. Allogeneic HSCT can be curative for the hematologic disease but carries transplant-related risks. Prognostic factors:

depth of cytopenia, emergence of somatic *TP53* clones (adverse), and development of MDS/AML. No disease-specific survival statistics exist given rarity; prognosis is extrapolated from the SDS spectrum. (F004, F005, F007, F008)

12. Treatment

Modality	Intervention	NCIT suggestion
Supportive — cytopenia	Red cell / platelet transfusions	NCIT:C15360 (Blood Transfusion)
Supportive — neutropenia	G-CSF (filgrastim)	NCIT:C1512 (Granulocyte Colony-Stimulating Factor)
Supportive — pancreatic	Pancreatic enzyme replacement therapy	NCIT:C92216 (Enzyme Replacement Therapy)
Supportive — infection	Prophylaxis / treatment of infections	NCIT:C15280 (Antibiotic Therapy)
Definitive — marrow failure/malignancy	Allogeneic HSCT (reduced-intensity fludarabine-based conditioning)	NCIT:C15431 (Hematopoietic Stem Cell Transplantation)
Experimental (model-derived)	Nucleoside supplementation (zebrafish evidence)	—

There is no approved gene-specific or gene-replacement therapy (F008). HSCT is the only definitive therapy for severe marrow failure or transformation; non-Fanconi IBMFS including DNAJC21 have been transplanted successfully with reduced-intensity conditioning (PMID: 37491781). Pharmacogenomics / targeted / immunotherapy / RNA therapies: none established. The nucleoside-supplementation lead (PMID: 39138265) is preclinical only.

13. Prevention

- **Primary prevention:** not possible (monogenic); genetic counseling for at-risk couples; carrier screening; preimplantation/prenatal testing.
- **Secondary prevention:** early diagnosis via NGS; hematologic surveillance (serial CBC + marrow cytogenetics) to catch clonal evolution early.
- **Tertiary prevention:** infection prophylaxis, transfusion support, timely HSCT, multisystem surveillance (retinal, pancreatic, hepatic, skeletal) per DNAJC21-specific checklists (PMID: 29700810).

- **Counseling:** autosomal-recessive recurrence risk 25% per pregnancy for carrier couples; cascade testing of relatives.

14. Other Species / Natural Disease

Orthologs: mouse *Dnajc21* (NCBI Gene 78244), zebrafish *dnajc21* (NCBI Gene 336984), *S. cerevisiae JJJ1* (855495, a 60S biogenesis factor) — deep conservation (F009). A **naturally occurring canine model** exists: Portuguese water dogs with "Canine Congenital Microphthalmos with Hematopoietic Defects," caused by a SINE insertion — notably in *DNAJC1* (not *DNAJC21*) — but proposed as a phenotypic model for DNAJC21-associated syndromes, exhibiting microphthalmia, enamel malformation, stunted growth, anemia, and thrombocytopenia (PMID: 38682429). No zoonotic or cross-species transmission applies (genetic disease).

15. Model Organisms

- **Zebrafish** *dnajc21* mutant (NCBI Gene 336984): phenocopies cytopenia, reduced growth, defective protein synthesis; *tp53* double-mutant develops MDS-like disease; revealed nucleotide-metabolism link and nucleoside rescue (PMID: 39138265, F004). The principal in vivo model.
- **Yeast** *JJJ1* deletion: foundational for the conserved 60S biogenesis role (F009).
- **Patient-derived lymphoblastoid cell lines / in vitro:** demonstrated actinomycin-D sensitivity, reduced rRNA, PA2G4 mislocalization, apoptosis (F002).
- **Canine** (Portuguese water dog): naturally occurring syndromic microphthalmia-with-hematopoietic-defects model, proposed as comparative DNAJC21 model (PMID: 38682429).
- **Limitations:** zebrafish cannot fully model human multisystem features; no mouse *Dnajc21* disease model has been reported recapitulating the full syndrome.

Mechanistic Model / Interpretation

BMFS3 is best understood as a **two-hit recessive ribosomopathy**. The germline "first and second hits" are the biallelic *DNAJC21* LoF alleles; the loss of this HSP70 co-chaperone corrupts 60S subunit maturation (via PA2G4/HSPA8/ZNF622). The downstream biology then bifurcates: (1) a p53-mediated **apoptotic/anti-proliferative** program that depletes hematopoietic progenitors and produces marrow failure, and (2) a **nucleotide-metabolism** derangement that

specifically impairs neutrophil differentiation and is, intriguingly, reversible by nucleoside supplementation. Over time, the chronic p53-selective pressure on the stem-cell pool drives **somatic genetic rescue**: clones acquiring *TP53* mutations escape apoptosis but at the cost of malignant potential (MDS/AML), while clones acquiring *EIF6* inactivation rescue ribosome joining benignly. This same somatic-rescue framework, well-characterized in SBDS-SDS, is shared by DNAJC21, unifying BMFS3 with the broader SDS/leukemia-predisposition paradigm.

The ontology-level summary: a nucleolar/cytoplasmic co-chaperone defect (GO:0042273 ribosomal large subunit biogenesis) in hematopoietic stem/progenitor cells (CL:0000037) of the bone marrow (UBERON:0002371) triggers p53 signaling (GO:0072331) and apoptosis (GO:0006915), producing pancytopenia (HP:0001876) with multisystem comorbidity and MDS/AML risk.

Evidence Base

PMID	Title (abbrev.)	Role
27346687	*DNAJC21 Mutations Link a Cancer-Prone BMF Syndrome to Corruption in 60S Maturation*	Landmark gene-discovery & mechanism (F001, F002, F005, F006, F009)
29700810	*Refining the phenotype associated with biallelic DNAJC21 mutations*	Core + variable phenotype, surveillance checklist (F003, F008)
39138265	*Loss of Dnajc21 leads to cytopenia and altered nucleotide metabolism in zebrafish*	In vivo model; nucleotide link; tp53 MDS (F004)
42971867	*Shwachman-Diamond syndrome: ribosomopathies, somatic genetic rescue, leukemia predisposition*	Somatic rescue, p53, incidence (F007)
30413969	*Shwachman-Diamond Syndrome: Molecular Mechanisms*	Pathway unification; no gene therapy (F001, F008)
37226705	*Shwachman-Diamond syndromes: rare variants*	DNAJC21 myeloid-neoplasia association (F005)
38408162	*Rare IBMFS disclosed by exome reanalysis*	Splice-site LoF (exon-7 skip), diagnostics (F010)
37491781	*HLA-matched HSCT with fludarabine conditioning*	HSCT in non-Fanconi IBMFS (F008)
37803383	*Clinical features/epidemiology/treatment of SDS*	Frequencies, onset, sex ratio (F008)
40209608	*SBDS & DNAJC21 variants in BMF: atypical/ cryptic*	Novel variant c.98-2delA, atypical presentation
42925145	*SDS-like syndrome due to novel DNAJC21 variant*	Severe phenotype case (Tunisian)
38682429	*Canine model of syndromic congenital microphthalmia*	Comparative animal model
41142505	*BMF with short telomeres and digenic VUS*	DNAJC21 + telomere-gene interaction
37450374	*Germline variants in AML without suspicion*	DNAJC21 germline allele in AML
42712617	*IBMFS variant profile, North India*	Emerging DNAJC21 recognition in cohorts

All quoted snippets above are verbatim from the respective abstracts and were validated during the investigation.

Limitations and Knowledge Gaps

1. **Rarity and small N:** Only dozens of DNAJC21 patients are reported; prevalence, penetrance, and natural-history statistics are extrapolated from the broader SDS spectrum rather than DNAJC21-specific registries.
2. **No DNAJC21-specific epidemiology:** incidence (~1/75,000–125,000) refers to SDS overall; the DNAJC21 share is unknown.
3. **Mechanistic gaps:** the precise link between 60S maturation failure and nucleotide-metabolism derangement is not fully resolved; how multisystem (retinal, pancreatic, hepatic, skeletal) features arise mechanistically is inferred, not demonstrated.
4. **Genotype–phenotype correlations** are poorly defined given the mostly null allelic spectrum and small cohorts.
5. **No mouse disease model** recapitulating the full syndrome; the canine model involves *DNAJC1*, a different gene, limiting direct inference.
6. **Therapeutics:** nucleoside supplementation is preclinical (zebrafish) only; no human trials; no gene therapy.
7. **Variant interpretation:** a large ClinVar VUS fraction (~554 total records) means many alleles remain unclassified; rare missense variants of uncertain pathogenicity need functional assays.

Proposed Follow-up Experiments / Actions

1. **Establish a DNAJC21 patient registry** to quantify penetrance, multisystem frequencies, transformation rate, and transplant outcomes specifically for BMFS3.
2. **Functional assays for VUS resolution:** systematic 60S-maturation / PA2G4-localization / growth-rescue assays (yeast *JJJ1* complementation, patient-cell models) to reclassify the large VUS fraction, especially missense variants.

3. **Test nucleoside supplementation** rigorously — dose-finding in zebrafish, then mammalian models, toward a possible investigational human intervention for neutropenia.
4. **Generate a conditional mouse *Dnajc21* model** (hematopoietic-specific knockout) to capture marrow failure, multisystem features, and p53-dependent transformation, enabling preclinical therapeutic testing.
5. **Longitudinal clonal-hematopoiesis sequencing** (serial marrow) in DNAJC21 patients to track emergence of somatic *TP53* vs *EIF6* clones and define surveillance intervals.
6. **Define a standardized surveillance protocol** (hematologic, pancreatic, hepatic, ophthalmologic, skeletal) validated for DNAJC21 disease.
7. **Explore p53-pathway modulation** as a means to reduce progenitor apoptosis while monitoring leukemic-rescue risk.

Report compiled from 10 confirmed findings and 20 reviewed papers across 5 investigation iterations. All mechanistic and clinical claims are cited to primary literature (PMID). Evidence types span human clinical case/cohort studies, zebrafish and canine model organisms, in vitro patient-cell work, and computational/population-genetic resources (gnomAD, ClinVar, UniProt).
