# SHILCA Syndrome: A Comprehensive Disease Characteristics Report

**Disease:** SHILCA Syndrome (Spondylo-epiphyseal dysplasia, sensorineural Hearing loss, Impaired Intellectual development, and Leber Congenital Amaurosis) **MONDO ID:** MONDO:0031007 · **OMIM:** 619260 · **Orphanet:** 611207 · **Category:** Mendelian (autosomal recessive) **Causal gene:** *NMNAT1* (1p36.22; HGNC:17877; NCBI Gene 64802)

## Summary

SHILCA syndrome is an **ultra-rare autosomal recessive multisystem disorder** first delineated in 2020, defined by the tetrad of **S**pondylo-epiphyseal dysplasia, sensorineural **H**earing loss, **I**mpaired intellectual development (with brain MRI anomalies), and **L**eber **C**ongenital **A**maurosis (SHILCA). It is caused by **biallelic hypomorphic (dosage-reducing) variants in *NMNAT1***, the gene encoding the nuclear isoform of nicotinamide mononucleotide adenylyltransferase, the enzyme that catalyzes the terminal step of $NAD^+$ biosynthesis. The archetypal mutation is an **Alu-mediated intragenic partial duplication** (c.299+526_*968dup) that reduces, but does not abolish, NMNAT1 expression — a critical point, because complete loss of NMNAT1 is embryonic-lethal in mice. The disorder is extraordinarily rare: only approximately four patients from three families** have been reported worldwide (PMID: 32533184, PMID: 33668384).

Mechanistically, reduced NMNAT1 function lowers **nuclear $NAD^+$**, which compromises PARP1-dependent DNA repair and sirtuin (SIRT1)-dependent stress adaptation and redox buffering. In the best-studied tissue — the retina — this converges on the progressive accumulation of the oxidative DNA adduct **8-oxo-dG**, triggering apoptotic photoreceptor loss. The same $NAD^+$-dependent vulnerability is inferred to extend to other metabolically demanding, long-lived cells: central neurons and oligodendrocytes (explaining intellectual disability, hypomyelinating leukoencephalopathy, and cerebellar hypoplasia), cochlear hair cells (sensorineural deafness), and chondrocytes (skeletal dysplasia). *NMNAT1* sits at the center of a broad **allelic series** that ranges from isolated non-syndromic Leber congenital amaurosis (LCA9) and cone/cone-rod dystrophy at the mild end, through hereditary spastic paraplegia, to the severe syndromic SHILCA phenotype.

There is **no approved disease-modifying therapy**; management is entirely supportive and multidisciplinary (low-vision/blindness rehabilitation, cochlear implants, developmental/physical/occupational/speech therapy, orthopedic and dental care), coupled with autosomal-recessive genetic counseling (25% sibling recurrence risk). However, AAV-mediated *NMNAT1* gene augmentation preserves retinal structure and function in mouse models, and the oxidative-DNA-damage mechanism, $NAD^+$-precursor supplementation, and SARM1 inhibition define rational, actively developing therapeutic avenues. A key diagnostic lesson is that SHILCA is a **"WES-negative" structural/splice disorder** that evades standard whole-exome sequencing and requires RNA-seq plus (ideally long-read) whole-genome sequencing to solve.

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## 1. Disease Information

**Overview.** SHILCA is a Mendelian, autosomal recessive, congenital multisystem syndrome combining a severe inherited retinal dystrophy (Leber congenital amaurosis) with sensorineural hearing loss, intellectual disability/brain anomalies, and a severe skeletal (spondylo-epiphyseal) dysplasia. It was first described by Bedoni et al. in 2020 in three children from two unrelated Italian families "presenting with a previously unrecognized autosomal recessive disorder that included a severe form of spondylo-epiphyseal dysplasia, sensorineural hearing loss, intellectual disability and Leber congenital amaurosis (SHILCA)" (PMID: 32533184).

**Key identifiers (Finding F010).**

| Resource | Identifier |
|---|---|
| MONDO | MONDO:0031007 |
| OMIM (disease) | 619260 (distinct from LCA9, OMIM 608553) |
| OMIM (gene *NMNAT1*) | 608700 |
| Orphanet | ORPHA:611207 |
| DOID | DOID:0112290 |
| GARD | 0018025 |
| MedGen | C1780157 |
| UMLS | C5543257 |
| ICD-10 / ICD-11 | No dedicated code (maps to generic hereditary retinal dystrophy H35.5 / 9B76) |
| MeSH | None (ultra-rare) |

**Synonyms:** "SHILCA syndrome"; "SHILCA"; full name "Spondyloepiphyseal dysplasia, sensorineural Hearing loss, Impaired intellectual development, and Leber Congenital Amaurosis."

**Source of information.** Knowledge of SHILCA is derived **entirely from individual patient case reports** and functional/model studies — aggregated disease-level resources are minimal, reflecting its ultra-rare Mendelian nature (F010).

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## 2. Etiology

**Primary cause (genetic).** SHILCA is a monogenic disorder caused by **biallelic (recessive) hypomorphic variants in *NMNAT1***. There is no environmental, infectious, or multifactorial contribution. The original families carried an **Alu-mediated partial duplication** of *NMNAT1*: "Short- and long-read whole-genome sequencing highlighted a duplication involving 2 out of the 5 exons of NMNAT1 main isoform (NM_022787.3), leading to the production of aberrant mRNAs" (PMID: 32533184) (F001).

**Genetic risk factors.** The disease-defining variants are the *NMNAT1* alleles themselves. The second reported patient was compound heterozygous for a novel splice variant and the recurrent duplication: "two heterozygous pathogenic variants in nicotinamide mononucleotide adenylyltransferase 1 (NMNAT1)... c.439+5G>T and c.299+526_*968dup" (PMID: 33668384) (F006). Because the phenotype requires residual NMNAT1 activity** (complete loss is lethal), the specific combination of hypomorphic alleles is itself the determinant of whether the syndromic (versus isolated ocular) phenotype emerges.

**Environmental risk / protective factors.** None established for the human disease. In mouse models, **light exposure exacerbates** photoreceptor degeneration in sensitized genotypes (compound heterozygous *Nmnat1^E257K/−*), suggesting phototoxic/oxidative stress can act as a gene–environment modifier of the ocular component (PMID: 29674119) (F007). No protective alleles or dietary/lifestyle protective factors are documented. Conceptually, **$NAD^+$-precursor availability** is a candidate modifiable factor given the biochemical defect, but this is unproven in SHILCA.

**Gene–environment interactions.** The clearest example is the **light-dependent exacerbation** of retinal degeneration in hypomorphic *Nmnat1* mice (F007). The underlying oxidative DNA-damage mechanism (8-oxo-dG accumulation) implies that oxidative load — metabolic and photic — modulates tissue vulnerability (F003).

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## 3. Phenotypes

SHILCA is a severe, congenital, multisystem phenotype. Orphanet classifies it as "a rare primary bone dysplasia" and expands the core tetrad with prominent CNS, neuromuscular, craniofacial, and dental features (F012).

| Phenotype | Type | HPO term | Onset / course | Frequency |
|---|---|---|---|---|
| Leber congenital amaurosis | Clinical sign (ophthalmic) | HP:0030512 | Congenital; rapid progression → stabilizes ~age 4 | Universal (cardinal) |
| Retinal degeneration | Clinical sign | HP:0000546 | Congenital, progressive | Universal |
| Macular/central retinal atrophy | Clinical sign | HP:0007401 | Coalesces into central scar by age 2 | Universal |
| Optic atrophy | Clinical sign | HP:0000648 | Early, progressive | Common |
| Nystagmus | Clinical sign | HP:0000639 | Infantile | Common |
| Hyperopia | Lab/refractive | HP:0000540 | Congenital | Universal in NMNAT1-LCA |
| Sensorineural hearing impairment | Clinical sign | HP:0000407 | Congenital/early | Cardinal |
| Intellectual disability | Behavioral/ cognitive | HP:0001249 | Developmental | Cardinal |
| Global developmental delay | Behavioral/ cognitive | HP:0001263 | Infantile | Common |
| Spondylo-epiphyseal dysplasia / platyspondyly | Physical/ skeletal | HP:0002655 | Congenital | Cardinal |
| Delayed CNS myelination | Imaging/ neurologic | HP:0002188 | Infantile | Reported |
| Leukoencephalopathy (hypomyelinating) | Imaging/ neurologic | HP:0002352 | Infantile | Reported |
| Cerebral hypoplasia | Imaging | HP:0006872 | Congenital | Reported |
| Cerebellar atrophy/ hypoplasia | Imaging | HP:0001272 | Infantile | Reported |
| Generalized hypotonia | Clinical sign | HP:0001252 | Early | Reported |

| Phenotype | Type | HPO term | Onset / course | Frequency |
|---|---|---|---|---|
| Ataxia | Clinical sign | HP:0001251 | Childhood | Reported |
| Depressed nasal bridge | Dysmorphic | HP:0005280 | Congenital | Reported |
| Wide mouth | Dysmorphic | HP:0000154 | Congenital | Reported |
| Abnormal dentition | Dental | HP:0000164 | Childhood | Reported |

**Ocular natural history (F008).** The retinal phenotype follows a stereotyped course: "All patients exhibited early-onset, rapidly progressive bilateral retinal degeneration with pronounced central involvement. The condition was characterized by multiple atrophic lesions that coalesced into a large central retinal scar by age 2. The condition stabilized around 4 years of age" (PMID: 39710161). Patients are hyperopic with **undetectable ERG and VEP** responses; most retain light-perception vision or better with minimal acuity deterioration after age 2.

**Quality of life impact.** The combination produces **deaf-blindness plus intellectual disability and skeletal/motor disability** — among the most severe possible multi-domain impairments — with lifelong dependence and need for specialized education and rehabilitation (F015). No disease-specific EQ-5D/SF-36/PROMIS data exist given the tiny patient count.

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## 4. Genetic / Molecular Information

**Causal gene.** *NMNAT1* (nicotinamide mononucleotide adenylyltransferase 1), chromosome **1p36.22**, ENSG00000173614, **HGNC:17877**, OMIM gene 608700, transcript NM_022787. It encodes the **nuclear** $NAD^+$-synthesizing enzyme (F002, F009, F011).

**Pathogenic variants in SHILCA.** - **c.299+526_*968dup** — recurrent Alu-mediated intragenic partial duplication (2 of 5 exons), producing aberrant mRNAs; reduces expression ~4-fold (hypomorphic, not null) (PMID: 32533184). - **c.439+5G>T** — novel non-canonical splice variant producing aberrant transcripts (second patient, compound heterozygous with the duplication) (PMID: 33668384).

All variants are **germline**, autosomal recessive, with a **loss/reduction-of-function (hypomorphic)** consequence — not gain of function (F009).

**Broader *NMNAT1* allelic series (F004).** *NMNAT1* exhibits a remarkable genotype–phenotype spectrum, with most pathogenic variants clustering in **exon 5**:

| Variant | cDNA | Phenotype | Reference |
|---|---|---|---|
| p.Glu257Lys | c.769G>A | Most common LCA9 hypomorph; incompletely penetrant | PMID: 24830548 |
| p.Val9Met | c.25G>A | Classic LCA9 (homozygous siblings) | PMID: 22842229 |
| p.Asn18Ser | c.53A>G | Milder, later-onset retinal dystrophy (with E257K) | PMID: 30004997 |
| p.Glu91Lys / E257K+N18S | — | Cone / cone-rod dystrophy with macular atrophy | PMID: 29184169 |
| p.E257K (homozygous) | c.769G>A | Hereditary spastic paraplegia | PMID: 36871412 |
| Duplication + splice | c.299+526_*968dup; c.439+5G>T | Syndromic SHILCA | PMID: 32533184, PMID: 33668384 |

The most common allele, **p.Glu257Lys**, "was observed in 38 of 106 alleles (35.8%)" and "is considered not fully penetrant" — it "was 80-fold less frequent in a homozygous state in patients... than predicted based on its heterozygosity frequency" (PMID: 24830548) (F004, F009).

**Population allele frequencies (gnomAD v4; F009).**

| Variant | rsID | Allele frequency | Notes |
|---|---|---|---|
| p.Glu257Lys | rs150726175 | ~$1.03\times10^{-3}$ (~0.1%; carrier ~1/485) | Common but reduced-penetrance hypomorph |
| p.Val9Met | rs387907294 | ~$3.4\times10^{-6}$ | Ultra-rare, deleterious |
| p.Asn18Ser | rs748902766 | ~$3.7\times10^{-5}$ | Rare |
| SHILCA duplication / splice | — | Not in gnomAD (private) | Explains extreme rarity |

This frequency structure — a common weak hypomorph alongside ultra-rare genuinely deleterious alleles — explains why isolated LCA9 is the predominant presentation while **syndromic SHILCA is vanishingly rare** (F009).

**Modifier genes / epigenetics / chromosomal abnormalities.** No specific modifier genes are established for SHILCA, though p.E257K has been proposed to act as a **modifier allele** in other LCA genetic subtypes (PMID: 24940029, supportive). No disease-specific DNA-methylation or histone-modification signature is defined. No large-scale chromosomal abnormality is involved — the lesion is a small **intragenic structural (duplication) variant** detectable only by WGS (F014).

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## 5. Environmental Information

SHILCA is a **purely genetic disorder**; no environmental, lifestyle, or infectious etiology applies. The only environmental modifier with experimental support is **light exposure**, which exacerbates retinal degeneration in sensitized hypomorphic *Nmnat1* mouse models (F007, PMID: 29674119). No toxin, radiation, occupational exposure, dietary factor, or infectious agent is implicated.

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## 6. Mechanism / Pathophysiology

### Ordered causal chain

1. **Biallelic hypomorphic *NMNAT1* variants** (Alu-mediated partial duplication ± splice variant) → **reduced *NMNAT1* mRNA/protein** (~4-fold downregulation in patient fibroblasts) — *demonstrated* (PMID: 32533184).
2. Reduced NMNAT1 enzyme → **decreased nuclear $NAD^+$ biosynthesis** (NMNAT1 catalyzes the terminal step, NMN + ATP → $NAD^+$) — *demonstrated biochemically* (F011, F013).
3. Lower nuclear $NAD^+$ → **impaired PARP1-dependent DNA repair and reduced SIRT1-dependent stress/redox adaptation** — *inferred* from NMNAT1–PARP1 interaction and $NAD^+$ biology (F011, F013).
4. Impaired repair + redox buffering → **accumulation of oxidative DNA damage (8-oxo-dG)** in vulnerable post-mitotic cells — *demonstrated in photoreceptors* (PMID: 41922335) (F003).
5. Oxidative DNA damage → **apoptotic cell loss** — *demonstrated in photoreceptors*; *inferred* for other tissues (F003).

6. **Branch point — tissue-specific manifestations** (driven by high metabolic/$NAD^+$ demand and cell longevity):
7. → **Photoreceptors** degenerate → Leber congenital amaurosis (*demonstrated*).
8. → **Central neurons / oligodendrocytes** → intellectual disability, hypomyelinating leukoencephalopathy, cerebellar hypoplasia (*inferred*).
9. → **Cochlear hair cells** → sensorineural hearing loss (*inferred*).
10. → **Chondrocytes / skeletal tissue** → spondylo-epiphyseal dysplasia (*inferred*).
11. Loss of NMNAT1's **$NAD^+$-independent chaperone/proteostasis function** may additionally compromise neuronal maintenance — *inferred* from invertebrate/in-vitro data (F002, F013, F016).

## Mechanistic detail

**Molecular pathway.** $NAD^+$ biosynthesis (KEGG hsa00760 nicotinamide/nicotinate metabolism; Reactome NAD biosynthesis): NMN/NaMN + ATP → $NAD^+$, catalyzed by NMNAT1, feeding **PARP1** (DNA repair) and **sirtuin/SIRT1** signaling (F011, F013). NMNAT1 "catalyzes the final step in NAD+ biosynthesis and represents the major nuclear isoform of the mammalian NMNAT family," and $NAD^+$ "supports redox reactions, DNA repair, chromatin regulation, stress adaptation, inflammation, and neuronal maintenance" (PMID: 42646333) (F013).

**Protein dysfunction.** NMNAT1 (UniProt Q9HAN9) is a **279-amino-acid nuclear homohexameric enzyme** (PDB 1KKU) that forms $NAD^+$ from NMN + ATP (and deamido-$NAD^+$ from NaMN), physically interacts with **PARP1**, and localizes to the nucleus (GO:0005634) (F011). Hypomorphic alleles reduce enzyme dosage rather than abolishing activity; NMNAT1 also "acts as a chaperone that protects against neuronal activity-induced degeneration" (PMID: 22842229).

**Cellular processes & tissue damage.** The demonstrated process is **oxidative DNA damage → apoptosis**: "reduced NMNAT1 enzyme function due to the p.V9M mutation leads to DNA damage in PRs, characterized by the progressive accumulation of the oxidative DNA adduct 8-oxo-dG" preceding apoptotic photoreceptor loss (PMID: 41922335) (F003). NMNAT1 dysfunction is more broadly linked to "aging-associated genomic instability, neuroinflammation, synaptic impairment, retinal degeneration" (PMID: 42646333) (F013).

**Why photoreceptors first?** NMNAT1 is ubiquitously expressed, yet reduced function preferentially injures photoreceptors — implicating their exceptionally high metabolic and $NAD^+$ demand and light-driven oxidative load (F003).

### Ontology suggestions

- **GO biological process:** NAD biosynthetic process (GO:0009435); nicotinamide-nucleotide adenylyltransferase activity (GO:0000309); DNA repair; apoptotic process.
- **GO cellular component:** nucleus (GO:0005634).
- **CL cell types:** retinal photoreceptor cell (CL:0000210); cochlear hair cell (CL:0000202); oligodendrocyte (CL:0000128); chondrocyte (CL:0000138); neuron (CL:0000540).
- **CHEBI:** $NAD^+$ (CHEBI:57540); NMN (CHEBI:16171); ATP (CHEBI:30616); deamido-$NAD^+$/NaAD (CHEBI:18304).

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## 7. Anatomical Structures Affected

**Organ level.** - **Primary:** eye/retina, inner ear/cochlea, central nervous system (cerebrum, cerebellum, white matter), skeleton (vertebral column, long-bone epiphyses). - **Body systems:** nervous (CNS + special senses), musculoskeletal, sensory (visual, auditory).

**Tissue and cell level (F012).**

| Structure | UBERON | Affected cell type | CL term |
|---|---|---|---|
| Retina / photoreceptor layer | UBERON:0000966 | Retinal photoreceptor cell | CL:0000210 |
| Cochlea / inner ear | UBERON:0001844 | Cochlear hair cell | CL:0000202 |
| Cerebral white matter | UBERON:0002316 | Oligodendrocyte | CL:0000128 |
| Cerebellum | UBERON:0002037 | Neuron | CL:0000540 |
| Vertebral column | UBERON:0001130 | Chondrocyte | CL:0000138 |
| Epiphysis of long bones | UBERON:0000958 | Chondrocyte | CL:0000138 |

**Subcellular level.** The primary compartment is the **nucleus (GO:0005634)**, where NMNAT1 synthesizes $NAD^+$ and interacts with PARP1 (F011). Downstream oxidative DNA damage affects **nuclear genomic DNA**.

**Localization / lateralization.** Retinal degeneration is **bilateral** with **pronounced central (macular) involvement**, coalescing into a central scar (PMID: 39710161) (F008). CNS involvement is diffuse/bilateral (leukoencephalopathy, cerebral/cerebellar hypoplasia); skeletal involvement is generalized/axial (platyspondyly, epiphyseal) (F012).

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## 8. Temporal Development

**Onset. Congenital.** The retinal phenotype is present at birth (Leber congenital amaurosis), and skeletal, auditory, and neurodevelopmental features manifest in infancy (F008, F012, F015).

**Progression (ocular).** A distinctive **triphasic** course: congenital severe deficit → rapid progression with atrophic lesions coalescing into a central scar by age 2 → **stabilization around age 4** (PMID: 39710161) (F008). This pattern distinguishes NMNAT1-LCA from many other LCA genotypes.

**Progression (systemic).** Intellectual disability, hearing loss, and skeletal dysplasia are **chronic, lifelong, non-remitting**. Hypomyelinating leukoencephalopathy and cerebellar hypoplasia imply ongoing neurological morbidity (F012, F015).

**Patterns.** No spontaneous or treatment-induced remission. The ocular **critical window** for intervention is the first years of life, before photoreceptor loss is complete — relevant to the stabilization-by-age-4 natural history and to gene-therapy timing (F008, F005).

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## 9. Inheritance and Population

**Epidemiology. Ultra-rare.** Approximately **four patients from three families** have been reported worldwide (three original Italian patients plus one Spanish patient) (F001, F006). No reliable prevalence/incidence figures exist; it is below Orphanet's reporting thresholds. The extreme rarity is explained by the requirement for two ultra-rare deleterious hypomorphic alleles (F009).

**Inheritance. Autosomal recessive**, with full penetrance for the biallelic genotypes described. Reported genotypes: homozygous partial duplication (consanguineous/shared-haplotype Italian families) and compound heterozygous duplication + splice variant (F001, F006). Recurrence risk for carrier couples is **25% per pregnancy** (F015).

**Penetrance / expressivity.** The syndromic SHILCA genotypes are penetrant. By contrast, the common *NMNAT1* allele **p.E257K is incompletely penetrant** (PMID: 24830548), and the overall allelic series shows **wide expressivity** (isolated LCA → cone-rod dystrophy → HSP → syndromic SHILCA), governed by residual enzyme activity (F004).

**Founder effects / consanguinity.** The original Italian families shared an identical haplotype across a 4.76 Mb autozygous region, consistent with a **shared ancestral allele / consanguinity-related homozygosity** (F001). No broad founder population is defined.

**Carrier frequency.** For deleterious SHILCA alleles, carrier frequency is essentially unmeasurable (private variants not in gnomAD). The common hypomorph p.E257K has a carrier frequency of ~1/485, but this allele alone does not cause SHILCA (F009).

**Demographics.** Reported patients are of European (Italian, Spanish) ancestry; no sex bias is evident (autosomal). Age at report was very young (~2 years) (F006, F015).

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## 10. Diagnostics

**Key diagnostic lesson (F014).** SHILCA is a **WES-negative structural/splice disorder**. In the index families, "whole-exome sequencing failed to identify any shared rare coding variants, in this region or elsewhere"; the diagnosis was reached only because "we then determined the transcriptome of patients' fibroblasts by RNA sequencing, followed by additional whole-genome sequencing experiments" (PMID: 32533184).

**Recommended diagnostic pathway.** 1. **Clinical gestalt** — recognize the LCA + sensorineural hearing loss + skeletal dysplasia + intellectual disability combination. 2. **Ophthalmic workup** — ERG/VEP (undetectable), OCT (outer-retinal disruption, RPE atrophy), fundus autofluorescence, fluorescein angiography (central hypofluorescence with visible choroidal vasculature) (PMID: 39710161) (F008). 3. **Brain MRI** — hypomyelination/leukoencephalopathy, cerebellar hypoplasia (F012). 4. **Skeletal survey** — spondylo-epiphyseal dysplasia, platyspondyly (F012). 5. **Molecular testing** — *NMNAT1* sequencing / IRD gene panel first; **if negative despite strong phenotype, escalate to WGS (short + long read) and/or fibroblast RNA-seq** to detect structural/splice variants (F014).

**Biomarkers.** No validated circulating biomarker; research assays include reduced NMNAT1 transcript/protein and increased 8-oxo-dG (mechanistic, not clinical) (F003, F014).

**Clinical criteria / differential diagnosis.** No formal criteria exist. Differentials include other syndromic LCAs and other causes of deaf-blindness with skeletal dysplasia; the distinctive NMNAT1-LCA retinal natural history (central scar by age 2, stabilizing by age 4) plus the specific multisystem combination point to SHILCA.

**NCIT terms:** Whole Genome Sequencing (C101294); RNA Sequencing (C101295); Whole Exome Sequencing (C101293).

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## 11. Outcome / Prognosis

**Overall (F015).** SHILCA is a congenital, chronic, non-remitting disorder producing **lifelong severe multi-domain disability**: profound early blindness, permanent sensorineural deafness, intellectual disability, and skeletal dysplasia (i.e., deaf-blindness plus ID plus motor/skeletal impairment).

**Visual prognosis.** Profound from birth; "most patients maintained light perception vision or better, with minimal deterioration of visual acuity after the age of 2" (PMID: 39710161) (F015). No meaningful spontaneous visual recovery.

**Survival/mortality.** Not quantifiable given ~4 reported patients; youngest described at ~age 2, no disease-specific mortality figure. Severe hypomyelinating leukoencephalopathy, hypotonia, and ataxia imply substantial morbidity (F015).

**Morbidity / function.** Combined sensory (vision + hearing), cognitive, and motor/skeletal disability; high lifelong care dependency.

**Prognostic factors.** Residual NMNAT1 activity (genotype severity) is the principal determinant of where a patient falls on the allelic spectrum (F004).

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## 12. Treatment

**Current standard — supportive only (F015).** There is **no approved disease-modifying therapy**, and "no human trial has yet established efficacy for an NMNAT-1-directed neurological therapy" (PMID: 42646333) (F013). Management is multidisciplinary: - **Sensorineural hearing loss:** cochlear implants/hearing aids; auditory-verbal therapy (NCIT: Cochlear Implant C16623). - **Vision:** low-vision/blindness rehabilitation, special education. -

**Neurodevelopment / hypotonia / ataxia:** developmental, physical, occupational, and speech therapy (NCIT: Physical Therapy C15415). - **Skeletal dysplasia:** orthopedic surveillance and management of spinal/joint disease. - **Dental care** for irregular dentition. - **Genetic counseling** (NCIT: Genetic Counseling C15671; Supportive Care C15346).

**Advanced / experimental therapeutics (preclinical; F005).** - **AAV gene augmentation:** "Gene Therapy Preserves Retinal Structure and Function in a Mouse Model" of NMNAT1-associated disease, where "no treatment is available" (PMID: 32775493). Photoreceptor-targeted expression is sufficient: "Expression of NMNAT1 in the photoreceptors is sufficient to prevent" degeneration (PMID: 37214313) — defining a photoreceptor-autonomous target. - **Antioxidant / DNA-damage-targeted approaches:** the 8-oxo-dG oxidative-DNA-damage mechanism was explicitly flagged as "a therapeutic opportunity" (PMID: 41922335). - **NAD-pathway strategies:** "Current therapeutic approaches include SARM1 inhibitors in clinical trials, gene therapy, and NAD precursor supplementation" (PMID: 42341897) (F005).

**Pharmacogenomics.** Not applicable (no disease-specific pharmacotherapy).

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## 13. Prevention

Because SHILCA is **purely genetic and congenital, primary prevention is not possible** by lifestyle/environmental means (F015).

- **Genetic counseling (primary preventive tool):** autosomal recessive counseling with **25% sibling recurrence risk**; cascade carrier testing once both familial *NMNAT1* alleles are identified.
- **Reproductive options: prenatal diagnosis** and **preimplantation genetic testing for monogenic disease (PGT-M)** are available to known carrier couples (F015).
- **Secondary prevention:** early ophthalmic, audiologic, neurodevelopmental, and skeletal surveillance to optimize supportive intervention (cochlear implantation, low-vision rehabilitation, early developmental therapy) within critical developmental windows.
- **Tertiary prevention:** orthopedic monitoring to prevent/limit complications of spondylo-epiphyseal dysplasia; management of leukoencephalopathy-related morbidity.
- **Immunization / public-health / environmental interventions:** not applicable.

**NCIT:** Genetic Counseling (C15671).

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## 14. Other Species / Natural Disease

**Taxonomy and orthologs (F016).** *NMNAT1* is deeply conserved:

| Species | NCBI Taxon | Gene | NCBI Gene ID |
|---|---|---|---|
| Human | 9606 | *NMNAT1* | 64802 |
| Mouse | 10090 | *Nmnat1* | 66454 |
| Zebrafish | 7955 | *nmnat1* | — |
| *Drosophila* | 7227 | *Nmnat*/CG13645 | — |

The NMNAT enzyme family is conserved to yeast (F016).

**Natural disease. No naturally occurring animal equivalent of SHILCA is cataloged in OMIA** — all animal disease models are engineered (F016). No companion-animal or wildlife natural counterpart, and no zoonotic/cross-species transmission applies.

**Comparative biology / conserved neuroprotection.** NMNAT's neuroprotective role is evolutionarily conserved. In *Drosophila*, "in vivo neuronal expression of mutated nmnat shows that enzymatically inactive NMNAT protein retains strong neuroprotective effects and rescues the degeneration phenotype caused by loss of nmnat" (PMID: 17132048) — evidence for an $NAD^+$-independent chaperone function. In mammals, the WldS fusion (Ube4b–Nmnat1) delays axon degeneration, and "increased Nmnat activity is responsible for the axon-sparing activity of the Wlds protein," with increased nuclear NAD biosynthesis and SIRT1 activation preventing axonal degeneration (PMID: 15310905) (F016).

## 15. Model Organisms

**Mouse models (primary; F007).**

| Model | Phenotype | Interpretation |
|---|---|---|
| *Nmnat1* germline knockout | Embryonic lethal | Complete loss incompatible with life → SHILCA requires hypomorphic allele (F002) |
| *Nmnat1^E257K/E257K* knock-in | No morphologic/functional retinal defect to 1 yr, even after light damage | E257K is a weak, reduced-penetrance hypomorph (PMID: 29674119) |
| *Nmnat1^E257K/–* compound het | Photoreceptor defects, exacerbated by light | Demonstrates dosage-dependence & gene–environment (light) interaction |
| Retina-specific conditional KO | Photoreceptor degeneration before terminal differentiation | NMNAT1 needed for retinal development and maintenance |
| AAV-*NMNAT1* gene therapy | Preserves retinal structure/ function | Proof-of-concept therapy (PMID: 32775493) |
| Photoreceptor-specific NMNAT1 expression | Prevents degeneration | Photoreceptor-autonomous target (PMID: 37214313) |
| p.V9M model | 8-oxo-dG accumulation → apoptosis | Oxidative DNA-damage mechanism (PMID: 41922335) |

**Invertebrate models.** *Drosophila Nmnat* mutants cause rapid activity-dependent neurodegeneration; enzymatically inactive NMNAT still rescues, demonstrating a chaperone function (PMID: 17132048) (F016).

**Model characteristics & limitations.** Mouse models **recapitulate the retinal (ocular) component** of SHILCA well and have validated both mechanism (oxidative DNA damage) and therapy (gene augmentation). However, **no published model recapitulates the full multisystem SHILCA phenotype** (skeletal dysplasia + hearing loss + leukoencephalopathy together); modeling to date has focused on the retina (F007, F016). Dosage is critical — null alleles are lethal, so SHILCA modeling requires hypomorphic/conditional strategies.

**Resources:** MGI (mouse *Nmnat1*, Gene 66454); FlyBase (*Nmnat*); ZFIN (*nmnat1*).

## Mechanistic Model (Synthesis)

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Biallelic hypomorphic NMNAT1 variants
(Alu-mediated partial duplication ± splice variant; germline, AR)
           │  demonstrated (RNA-seq ~4x downregulation; WGS)
           ▼
Reduced NMNAT1 enzyme dosage  ──(residual activity preserved;
           │                      complete loss = embryonic lethal)
           ▼
Decreased NUCLEAR NAD+ biosynthesis (NMN + ATP → NAD+)
           │  demonstrated biochemically
           ▼
Impaired PARP1 DNA repair  +  reduced SIRT1 redox/stress adaptation   [inferred]
           ▼
Accumulation of oxidative DNA damage (8-oxo-dG)   [demonstrated in photoreceptors]
           ▼
Apoptosis of metabolically demanding, long-lived cells
  ├── Photoreceptors ........ Leber congenital amaurosis   [demonstrated]
  ├── Neurons/oligodendrocytes .. ID, leukoencephalopathy, cerebellar hypoplasia [inferred]
  ├── Cochlear hair cells ... sensorineural hearing loss   [inferred]
  └── Chondrocytes .......... spondylo-epiphyseal dysplasia [inferred]
```

The retinal arm of this chain is experimentally established end-to-end; the extra-ocular arms are mechanistically plausible extrapolations of the same $NAD^+$-deficiency logic applied to cells with high metabolic demand and limited renewal.

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# Evidence Base

| PMID | Title (abbrev.) | Contribution |
|---|---|---|
| 32533184 | *Alu-mediated duplication in NMNAT1 causes SHILCA* | **Defines the disease**; identifies the Alu-mediated partial duplication; establishes WES-negative, RNA-seq+WGS diagnosis (F001, F002, F014) |
| 33668384 | *New insights on the genetic basis of SHILCA* | **Second independent patient**; compound-het splice + duplication; replicates full phenotype (F006) |
| 22842229 | *NMNAT1 mutations cause LCA with macular/optic atrophy* | Establishes NMNAT1 as LCA9 gene; nuclear enzyme + chaperone role (F002, F011) |
| 41922335 / 40501637 | *Oxidative DNA damage drives apoptotic photoreceptor loss* | **Mechanism**: 8-oxo-dG accumulation → apoptosis; therapeutic opportunity (F003) |
| 24830548 | *Nonpenetrance of most frequent NMNAT1 LCA mutation* | p.E257K most common (35.8%), incompletely penetrant; allele-frequency logic (F004, F009) |
| 36871412 | *NMNAT1 and hereditary spastic paraplegia* | Extends allelic series beyond retina (F004) |
| 29184169 | *NMNAT1 variants cause cone/cone-rod dystrophy* | Broadens ocular allelic spectrum (F004) |
| 30004997 | *Milder later-onset NMNAT1 retinopathy* | Milder end of spectrum; genotype–severity link (F004) |
| 39710161 | *Natural history of NMNAT1-LCA* | **Ocular natural history**: rapid progression → stabilizes ~age 4 (F008, F015) |
| 29674119 | *NMNAT1 E257K mouse model* | Dosage-dependence; E257K homozygotes asymptomatic; light exacerbation (F007) |
| 32775493 | *Gene therapy preserves retina in mouse model* | AAV gene augmentation proof-of-concept (F005) |
| 37214313 | *NMNAT1 in photoreceptors sufficient to prevent degeneration* | Photoreceptor-autonomous therapeutic target (F005, F007) |
| 42341897 | | NAD-pathway/SARM1 therapeutic landscape (F005) |

| PMID | Title (abbrev.) | Contribution |
|---|---|---|
| | *Programmed axon degeneration gene variants* | |
| 42646333 | *NMNAT1 and NAD review (2026)* | NMNAT1 as terminal nuclear NAD+ enzyme; no proven human therapy (F013) |
| 17132048 | *Drosophila NMNAT maintains neural integrity* | Conserved, NAD+-independent neuroprotection (F016) |
| 15310905 | *Nuclear NAD biosynthesis + SIRT1 prevent axon degeneration* | Mammalian conservation of neuroprotective NAD+ mechanism (F016) |

**Evidence-type caveat.** Several SHILCA/NMNAT1 citation snippets were flagged `[mismatch]` during validation (e.g., the exact variant-nomenclature quotes from P 33668384 and the NMNAT1-review quotes from P 42646333). The underlying claims are consistent with the papers' reported findings, but the verbatim snippets should be re-verified against the published abstracts before being entered as exact quotes in a knowledge base.

## Limitations and Knowledge Gaps

1. **Extreme rarity (n ≈ 4).** All clinical knowledge derives from ~4 patients in 3 families. Penetrance, expressivity, full phenotypic range, prognosis, survival, and natural history of the extra-ocular features are essentially uncharacterized.
2. **Extra-ocular mechanism is inferred, not demonstrated.** The oxidative-DNA-damage → apoptosis chain is proven only in photoreceptors. Its application to chondrocytes, cochlear hair cells, and oligodendrocytes is a reasonable but untested extrapolation.
3. **No multisystem model.** All animal models capture the retinal phenotype; none recapitulates the skeletal, auditory, and leukoencephalopathy triad simultaneously.

4. **No validated clinical biomarker** or formal diagnostic criteria; diagnosis relies on expert gestalt plus escalated genomic testing.
5. **No human therapeutic evidence.** Gene therapy and NAD-pathway strategies are preclinical/retina-focused; none addresses the systemic disease.
6. **Genotype–phenotype rules are incomplete.** Why specific hypomorphic combinations yield syndromic SHILCA versus isolated LCA9 is not quantitatively defined (residual-activity thresholds are hypothesized, not measured per allele).
7. **Citation-snippet mismatches** (above) require manual verification.

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## Proposed Follow-up Experiments / Actions

1. **International patient registry / GeneMatcher outreach** — aggregate additional SHILCA cases to define phenotype frequencies, natural history of extra-ocular features, and prognosis.
2. **Allele-resolved enzymatic assays** — quantify residual NMNAT1 activity/$NAD^+$ output for each hypomorphic allele (duplication, splice, E257K, V9M) to test the residual-activity-threshold model of genotype–phenotype correlation.
3. **Multisystem mouse model** — generate hypomorphic/compound-heterozygous *Nmnat1* alleles matching patient genotypes (e.g., humanized duplication) and phenotype the skeleton, cochlea, and brain, not just the retina.
4. **Mechanistic validation in extra-ocular cell types** — measure nuclear $NAD^+$, PARP1 activity, and 8-oxo-dG in patient-derived iPSC-chondrocytes, otic organoids, and oligodendrocytes to test whether the retinal mechanism generalizes.
5. **Therapeutic testing of $NAD^+$ precursors ± SARM1 inhibition** — assess whether systemic $NAD^+$ boosting (NR/NMN) or SARM1 inhibition mitigates extra-ocular degeneration in a multisystem model; the retina-focused AAV strategy cannot reach skeleton/CNS equally.
6. **Diagnostic protocol dissemination** — publish/endorse a tiered algorithm (IRD panel → WGS short+long read → fibroblast RNA-seq) so that WES-negative SHILCA cases are reliably solved.
7. **Verify flagged citation snippets** against source abstracts (P 33668384

P 37214313

)

P 42646333

before knowledge-base entry.

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*Prepared from 16 confirmed findings across 5 investigation iterations and 39 reviewed papers. Evidence spans human clinical case reports, mouse/Drosophila model organism studies, in-vitro biochemistry, and computational/population-genetic data.*

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