Lowry-Wood Syndrome (MONDO:0009191): A Comprehensive Disease Characteristics Report

MONDO: MONDO:0009191 · **Causal gene:** *RNU4ATAC* (RNA, U4atac small nuclear; HGNC:34140; gene OMIM 601428; chr 2q14.2) · **Orphanet:** ORPHA:2648 · **Category:** Mendelian, autosomal recessive

Summary

Lowry-Wood syndrome (LWS; MONDO:0009191) is an ultra-rare, autosomal-recessive skeletal dysplasia caused by biallelic loss-of-function variants in *RNU4ATAC*, a non-coding, single-exon gene on chromosome 2q14.2 (HGNC:34140; OMIM 601428) that is transcribed into the **U4atac small nuclear RNA (snRNA)** — a core component of the **minor (U12-dependent) spliceosome**. Although the disorder's descriptive synonym ("Multiple epiphyseal dysplasia with microcephaly and nystagmus") emphasizes the skeletal and ophthalmologic triad, the causal lesion is not in a cartilage or eye gene but in a housekeeping RNA required for excision of ~700–800 "minor" (U12-type) introns scattered across the genome. LWS represents the **mildest end** of a clinical spectrum of **RNU4ATAC-opathies** that also includes **Roifman syndrome (RS)** and the severe, often perinatally lethal **microcephalic osteodysplastic primordial dwarfism type 1 (MOPD1 / Taybi-Linder syndrome)**.

The defining clinical features of LWS are **multiple epiphyseal dysplasia** (causing short stature and joint/limb anomalies), **microcephaly**, **developmental delay / intellectual disability** (typically mild), and **eye involvement** (nystagmus and progressive retinal dystrophy). Across the broader RNU4ATAC-opathy spectrum, additional management-relevant features include **immune deficiency** (antibody deficiency, low B-cell subsets), **cerebral anomalies**, and **chilblain-like skin lesions**. Genotype–phenotype analyses show that severity is governed largely by **variant position within the U4atac RNA secondary structure**: the most severe MOPD1-causing variants cluster in the functionally constrained 5′ stem-loop critical for U4/U6.U5 tri-snRNP assembly, whereas milder LWS and RS variants are more dispersed.

The unifying molecular mechanism is **transcriptome-wide retention and mis-splicing of U12-type minor introns**, demonstrated by RNA-seq in patient cells and consistent across the spectrum. This minor-intron splicing defect depletes self-amplifying neural progenitors (producing microcephaly), disrupts chondro-osseous development (producing epiphyseal dysplasia and short stature), and secondarily perturbs ciliary function, JAK/STAT signaling, and type I interferon responses (contributing to immune and skin phenotypes). Diagnosis hinges on sequencing the non-coding *RNU4ATAC* exon — frequently missed by standard exome pipelines — with RNA-seq minor-intron-retention as a functional biomarker that enables variant reclassification. No disease-modifying therapy exists; management is supportive and multidisciplinary, with genetic counseling for the 25% recurrence risk.

Key Findings

Finding 1 — LWS is caused by biallelic variants in the non-coding minor-spliceosome gene *RNU4ATAC*

Exome sequencing across multiple families established that LWS results from **biallelic (homozygous or compound heterozygous) pathogenic variants in *RNU4ATAC***, which transcribes the U4atac snRNA of the minor (U12-dependent) spliceosome. Farach et al. (2018) first established the genetic cause, describing *"three patients with Lowry Wood syndrome with biallelic RNU4ATAC pathogenic variants"* and stating that their report *"is the first to establish the genetic cause for Lowry Wood syndrome"* (PMID: 29265708). Shelihan et al. (2018) confirmed the association, noting that *"Pathogenic variants in RNU4ATAC, an RNA of the minor spliceosome important for the excision of U12-dependent introns, have been recently associated with LWS"* (PMID: 30368667). *RNU4ATAC* has a single non-coding exon on chromosome 2q14.2. This is a human clinical/genetic finding.

Finding 2 — RNU4ATAC disorders form a severity spectrum governed by variant location, with LWS the mildest

The RNU4ATAC-opathies constitute a continuum of severity from **MOPD1 (most severe, frequently lethal)** through **Roifman syndrome** to **Lowry-Wood syndrome (mildest)**. Shelihan et al. (2018) analyzed all reported variants and found that *"FitCons scores for nucleotides mutated in the more severe MOPD are higher than RS or LWS and that they were more frequently located in the 5' Stem-Loop of the RNA critical for the formation of the U4/U6.U5*

tri-snRNP complex, whereas the variants are more dispersed in the other conditions" (PMID: 30368667). A recent integrated reevaluation confirms the spectrum *"whose severity ranges from the microcephalic osteodysplastic primordial dwarfism type 1 (MOPD1) to the milder Roifman syndrome"* (PMID: 41808109). Clinically the categories overlap substantially; one reported individual had *"a novel genotype and phenotype spanning all three disorders"* (PMID: 36622817), supporting the view of a single phenotypic continuum rather than discrete diseases.

Finding 3 — Core clinical phenotype: multiple epiphyseal dysplasia, microcephaly, short stature, developmental delay, and eye involvement

LWS is defined as *"a skeletal dysplasia characterized by multiple epiphyseal dysplasia associated with microcephaly, developmental delay and intellectual disability, and eye involvement"* (PMID: 30368667). In the largest RNU4ATAC-opathy cohort reported to date (n = 60), *"Core features in this cohort—present in most individuals assessed and varying in severity—include microcephaly, short stature, skeletal anomalies, developmental delay, cerebral anomalies, skin conditions, and immune deficiency"* (PMID: 42322193). Eye involvement in LWS prominently includes **nystagmus** (reflected in the descriptive synonym) and **progressive retinal dystrophy**.

Finding 4 — Mechanism: defective U4atac impairs the minor spliceosome, causing transcriptome-wide minor (U12-type) intron retention

The U4atac snRNA is *"a minor spliceosome component that is essential for minor intron splicing"* (PMID: 26522830). The minor spliceosome excises ~700–800 U12-dependent introns (~0.5–1% of all human introns) found in a functionally diverse set of genes. Pathogenic *RNU4ATAC* variants impair this machinery: RNA-seq of patient cells *"confirms extensive and specific defects of minor intron splicing"* (PMID: 26522830), and across the large cohort *"all individuals who underwent RNA-seq showed a consistent pattern of minor intron retention"* (PMID: 42322193). This minor-intron retention is the shared, upstream molecular consequence across the entire RNU4ATAC-opathy spectrum and provides a functional readout usable for variant reclassification.

Finding 5 — Secondary mechanisms: ciliary dysfunction, dysregulated JAK/STAT signaling, and type I interferon activation

Beyond the primary splicing defect, several downstream pathways are perturbed. (1) **Ciliary dysfunction:** U4atac depletion secondarily produces ciliary defects — *"Deficiency of the minor spliceosome component U4atac snRNA secondarily results in ciliary defects in human and zebrafish"* (PMID: 36802443) — linking minor-spliceosome deficiency to ciliopathy-like features. (2) **JAK/STAT signaling:** A *Drosophila* U4atac mutant shows reduced splicing of the JAK

homolog *hopscotch*; *"our work identifies alterations of Jak signaling as part of the pathogenesis of RNU4atac-opathy"* (PMID: 42463491), implicating JAK/STAT in hematopoietic/immune pathogenesis. (3) **Type I interferon:** RNU4ATAC patients commonly develop painful chilblain-like skin lesions; *"painful chilblain-like lesions are common in RNU4ATAC patients and are linked to dysregulated type I interferon signalling"* (PMID: 40415209).

Finding 6 — Immunodeficiency and progressive retinal dystrophy are recurrent, management-relevant features

Immune deficiency — antibody deficiency, low lymphocyte and B-cell subsets, impaired B-cell maturation — is characteristic of Roifman syndrome and is now recognized even in the severe MOPD1 end of the spectrum. A report of twin sisters emphasized B-cell anomalies in MOPD1 and underscored *"the importance of considering immunodeficiency in MOPDI management to reduce the risk of serious infectious episodes"* (PMID: 38837402). **Retinal dystrophy** in RNU4ATAC-Roifman syndrome is a generalized rod-cone dystrophy: in a deeply phenotyped cohort of 10 patients, all had abnormal ERG and *"nine showed generalized rod-cone dystrophy"* (PMID: 37225827), with nyctalopia common and progressive visual loss on follow-up. These findings justify immunologic and ophthalmologic surveillance in LWS.

Finding 7 — LWS is an autosomal recessive disorder, first described by Lowry and Wood (1975), and is ultra-rare

Lowry and Wood (1975) first described two boys with epiphyseal dysplasia, short stature, microcephaly, and nystagmus. Nevin et al. (1986) reported a second family, noting *"the second example of the syndrome first described by Lowry and Wood [1975] in two boys who had epiphyseal dysplasia, short stature, microcephaly, and nystagmus; one of these patients was mildly mentally retarded"* and concluding that *"The Lowry-Wood syndrome probably is an autosomal recessive trait"* (PMID: 3706411). Only a few dozen molecularly confirmed RNU4ATAC-opathy patients exist worldwide (60 in the largest cohort), making LWS ultra-rare with no formal prevalence estimate.

Finding 8 — Animal models recapitulate key features: minor-spliceosome loss causes microcephaly and limb micromelia

Model-organism work supports causality between minor-spliceosome dysfunction and the cardinal LWS phenotypes. Conditional inactivation of the minor spliceosome (Rnu11/U11 ablation) in developing mouse cortex demonstrated that *"Minor spliceosome inactivation causes microcephaly, owing to cell cycle defects and death of self-amplifying radial glial cells"*

(PMID: 30093551). In the limb, *"Loss of U11 small nuclear RNA in the developing mouse limb results in micromelia"* (PMID: 32665241), linking minor-spliceosome loss to skeletal dysplasia. A CRISPR *Drosophila* U4atac mutant reproduced growth/neurodevelopmental defects, immunodeficiency, and GI symptoms via mis-splicing of innate-immunity and hematopoiesis transcripts (PMID: 42463491), and zebrafish U4atac knockdown produced ciliary defects (PMID: 36802443).

Finding 9 — Diagnosis requires sequencing the non-coding *RNU4ATAC* exon; variants are frequently missed, and RNA-seq aids classification

Because *RNU4ATAC* is a single-exon non-coding gene, *"the bioinformatic prediction algorithms assessing the effect of sequence variants on splicing or protein function are irrelevant"* (PMID: 32628740), and variants *"are often overlooked in analysis because of their noncoding nature"* (PMID: 42322193). Some exome capture kits do not even target the gene — *"RNU4ATAC is not targeted by many commercially available exome capture kits"* (PMID: 37666272) — so whole-genome sequencing or targeted *RNU4ATAC* Sanger sequencing may be required; in one Chinese family, variants were identified only after WES was negative (PMID: 29370840). A cellular minor-intron splicing reporter assay (PMID: 32628740) and RNA-seq demonstrating minor intron retention provide functional evidence: *"In 6 individuals, RNA-seq enabled the reclassification of variants of uncertain significance as likely pathogenic"* (PMID: 42322193).

Finding 10 — RNU4ATAC disorders are molecularly and clinically distinct from PCNT-related MOPD type II

A critical differential-diagnosis point: the RNU4ATAC-opathies (MOPD1, Roifman, LWS) must be distinguished from the superficially similarly named **microcephalic osteodysplastic primordial dwarfism type II (MOPD II)**, caused not by a spliceosome RNA but by loss-of-function variants in **PCNT (pericentrin)**, a centrosomal protein. *"Loss-of-function variants of this gene are responsible for microcephalic osteodysplastic primordial dwarfism type II (MOPDII), a rare inherited autosomal recessive disorder"* (PMID: 37234811). MOPD II is distinguished by a **high risk of cerebral aneurysms and Moyamoya vasculopathy**; in one report *"The boy died at 8 years of age as a result of an intracranial hemorrhage due to a cerebral aneurism associated with the Moyamoya malformation"* (PMID: 37234811). This cerebrovascular risk belongs to PCNT-MOPD II, **not** to RNU4ATAC disorders — a distinction that affects surveillance and prognosis.

Detailed Report by Section

1. Disease Information

Overview. Lowry-Wood syndrome is an ultra-rare autosomal-recessive skeletal dysplasia (a "minor spliceosomopathy") characterized by multiple epiphyseal dysplasia, microcephaly, short stature, developmental delay/intellectual disability, and ophthalmologic abnormalities (nystagmus, retinal dystrophy). It is the mildest recognized presentation of the RNU4ATAC-opathy spectrum.

Key identifiers. | Resource | Identifier | |---|---| | MONDO | MONDO:0009191 | | Causal gene | *RNU4ATAC* (HGNC:34140; OMIM 601428; chr 2q14.2) | | Orphanet | ORPHA:2648 | | OMIM (disease) | Not formally recorded as a distinct phenotype MIM (LWS historically clinical; now within RNU4ATAC-opathy) | | ICD-10 | Q77.x (osteochondrodysplasia with defects of growth; best fit) | | MeSH | No dedicated LWS descriptor; indexed under osteochondrodysplasias/ dwarfism |

Synonyms: Lowry Wood syndrome; LWS; RNU4ATAC-related Lowry-Wood syndrome; Multiple epiphyseal dysplasia with microcephaly and nystagmus.

Information source: Derived from aggregated disease-level resources and small published case series/cohorts (individual-patient reports pooled into cohorts such as the n = 60 RNU4ATAC-opathy study), not from EHR-scale data.

2. Etiology

Causal factor: Purely **genetic** — biallelic (homozygous or compound heterozygous) loss-of-function variants in *RNU4ATAC* (PMID: 29265708). No environmental or infectious cause.

Genetic risk factors / modifiers: The principal determinant of phenotype severity is **variant position within the U4atac RNA secondary structure** — 5′ stem-loop variants (high FitCons constraint) produce severe MOPD1, while more dispersed variants produce milder LWS/RS (PMID: 30368667). Compound heterozygosity combining a "severe" and a "mild" allele can yield intermediate phenotypes. No separate susceptibility loci or distinct modifier genes have been established.

Environmental / protective factors and gene–environment interactions: None identified; not applicable for a fully penetrant Mendelian recessive disorder. Consanguinity increases the chance of homozygosity in affected families (relevant to recessive inheritance generally).

3. Phenotypes

Phenotype	HPO term (suggested)	Type	Onset	Frequency	Severity/ course
Multiple epiphyseal dysplasia	HP:0002656	Physical/ skeletal	Congenital/ childhood	Core (most)	Variable, chronic
Microcephaly	HP:0000252	Physical sign	Congenital/ postnatal	Core (most)	Static/ variable
Short stature	HP:0004322	Physical sign	Childhood	Core (most)	Chronic
Developmental delay / intellectual disability	HP:0001263 / HP:0001249	Behavioral/ cognitive	Childhood	Common (often mild in LWS)	Static
Nystagmus	HP:0000639	Clinical sign	Infancy/ childhood	Characteristic	Stable
Retinal dystrophy (rod-cone)	HP:0000510 / HP:0000548	Lab/clinical (ERG)	Childhood, progressive	Characteristic (RS end)	Progressive
Immune deficiency / antibody deficiency	HP:0002090 / HP:0004313	Laboratory	Childhood	Spectrum-dependent	Variable
Cerebral anomalies	HP:0002060	Imaging	Congenital	Common	Static
Chilblain-like skin lesions	HP:0011109	Physical	Variable	Common	Episodic

Quality-of-life impact is driven by short stature and skeletal/joint limitation (mobility), visual impairment (progressive retinal dystrophy), developmental/cognitive needs, and infection susceptibility from immune deficiency. Formal QoL instrument data (EQ-5D/SF-36) are not available for this ultra-rare disorder.

4. Genetic / Molecular Information

Causal gene: *RNU4ATAC* — non-coding, single-exon, transcribed into the ~130-nt U4atac snRNA; chr 2q14.2; HGNC:34140; OMIM 601428.

Pathogenic variants: All reported disease variants are single-nucleotide changes or small indels in the non-coding RNA; because there is no protein product, variant classes are described by location in the RNA structure rather than missense/nonsense terminology. Recurrent/illustrative variants include **n.51G>A** (the most frequent MOPD1-causative 5′ stem-loop variant), **n.50G>A** / **n.55G>A** (compound het in MOPD1-phenotype patients), **n.29T>A** (MOPD1 hotspot), and more dispersed variants in milder LWS/RS. Functional consequence is **loss of function** of U4atac, i.e., impaired minor spliceosome assembly. Pathogenic alleles are very rare/absent in gnomAD; carrier frequency is not well established (PMID: 32628740).

Variant origin: Germline. No somatic involvement.

Modifier genes / epigenetics / chromosomal abnormalities: No established modifier genes, epigenetic signatures, or large chromosomal rearrangements; CMA and karyotype are characteristically normal (the point variants are not detected by those methods) (PMID: 29370840).

5. Environmental Information

Not applicable. LWS is a monogenic recessive disorder with no known environmental, lifestyle, or infectious contributors. (Infections may be *consequences* of the associated immune deficiency — e.g., HHV-6–associated encephalopathy reported in a MOPD1 patient — but infection is not a cause of the disease.)

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. Biallelic loss-of-function variants in *RNU4ATAC* **lead to** a structurally/functionally defective U4atac snRNA.
2. Defective U4atac **impairs** assembly of the U4atac/U6atac.U5 tri-snRNP, the catalytic core of the **minor (U12-dependent) spliceosome**.
3. Impaired minor spliceosome **results in** failure to excise ~700–800 U12-type minor introns → **transcriptome-wide minor-intron retention and mis-splicing** (demonstrated by patient RNA-seq).

4. Minor-intron retention in affected transcripts **reduces** functional expression of the diverse minor-intron-containing genes (enriched in cell-cycle, DNA-replication, and signaling functions). 5a. In neural progenitors, this **causes** cell-cycle defects and death of self-amplifying radial glial cells → reduced neuron output → **microcephaly and developmental delay** (demonstrated in mouse Rnu11 models; inferred for humans). 5b. In the developing limb/skeleton, minor-spliceosome deficiency **disrupts** chondro-osseous development → **epiphyseal dysplasia, short stature, micromelia** (demonstrated in mouse U11 limb model; inferred for humans). 5c. (Branch) Secondary **ciliary dysfunction contributes to** skeletal/developmental and possibly retinal phenotypes (human + zebrafish). 5d. (Branch) Mis-splicing of **JAK/STAT pathway** transcripts **attenuates** cytokine signaling → impaired hematopoiesis/B-cell maturation → **immune deficiency** (Drosophila + patient data). 5e. (Branch) **Dysregulated type I interferon signaling produces** painful **chilblain-like skin lesions**.
5. The combined developmental and signaling defects **manifest** as the LWS clinical phenotype; variant position on the severity gradient **determines** whether the outcome is mild (LWS), intermediate (RS), or severe/lethal (MOPD1).

Upstream vs downstream: Steps 1–3 (variant → U4atac → minor-spliceosome failure → minor-intron retention) are upstream and shared across the entire spectrum. Steps 5a–5e are downstream, tissue-specific consequences.

Ontology suggestions: - GO biological process: mRNA splicing via spliceosome (GO:0000398), cell cycle (GO:0007049), neural progenitor proliferation, JAK-STAT signaling (GO:0007259), type I interferon signaling (GO:0060337), cilium assembly (GO:0060271). - Reactome: minor (U12-dependent) spliceosome pathway. - CL cell types: radial glial cell (CL:0000681), chondrocyte (CL:0000138), B cell (CL:0000236), rod (CL:0000604) / cone (CL:0000573) photoreceptor. - Subcellular (GO CC): spliceosomal complex (GO:0005681), nucleus/nuclear speckle; cilium (GO:0005929).

7. Anatomical Structures Affected

- **Skeletal system** (UBERON:0001434): epiphyses (UBERON:0002515), long bones, joints — multiple epiphyseal dysplasia, short stature.
- **Nervous system / brain** (UBERON:0000955): microcephaly, cerebral anomalies; cerebral cortex (UBERON:0000956) and radial glia affected.
- **Eye** (UBERON:0000970): retina (UBERON:0000966) — rod-cone dystrophy; oculomotor system — nystagmus.
- **Immune/hematopoietic system** (UBERON:0002405): B-lymphocyte compartment.

- **Skin** (UBERON:0002097): chilblain-like lesions, often acral/bilateral.
- **Lateralization:** skeletal and retinal involvement are characteristically **bilateral/symmetric**.

8. Temporal Development

- **Onset:** Congenital/prenatal for growth and microcephaly (intrauterine growth restriction in severe cases); skeletal dysplasia and nystagmus apparent in infancy/childhood.
- **Course:** Largely **static** for structural/developmental features, but **progressive** for the retinal dystrophy (progressive visual loss on follow-up) and episodic for chilblain-like skin lesions.
- **Duration:** Chronic/lifelong. In LWS (mild end), lifespan is not markedly curtailed; by contrast MOPD1 is frequently lethal in infancy/early childhood.
- **Critical period:** Fetal/early-postnatal neurodevelopment (radial glial proliferation window) is the key vulnerability period; no established intervention window exists.

9. Inheritance and Population

- **Inheritance:** Autosomal recessive (PMID: 3706411); recurrence risk 25% per pregnancy for carrier couples.
- **Penetrance/expressivity:** High penetrance for biallelic pathogenic genotypes, but **highly variable expressivity** governed by variant position and allele combination.
- **Epidemiology:** Ultra-rare; only a few dozen molecularly confirmed RNU4ATAC-opathy patients worldwide (60 in the largest cohort). No formal prevalence/incidence estimate.
- **Sex ratio:** No sex predilection (autosomal). **Consanguinity** elevates risk via homozygosity. No well-defined founder effects, though recurrent hotspot variants (e.g., n.51G>A) exist. Carrier frequency not reliably established.

10. Diagnostics

- **Genetic testing is definitive.** Because *RNU4ATAC* is non-coding and single-exon, protein/splice predictors do not apply and the gene is missed by many exome kits. Recommended approach: **whole-genome sequencing** or **targeted *RNU4ATAC* Sanger sequencing**, especially when WES is negative in a clinically suggestive patient (PMID: 37666272; PMID: 29370840).

- **Functional biomarker: RNA-seq demonstrating minor-intron retention** and a **cellular minor-intron splicing reporter assay** provide functional pathogenicity evidence and enable VUS reclassification (PMID: 42322193; PMID: 32628740).
- **Imaging:** Skeletal survey (epiphyseal dysplasia), brain MRI (microcephaly/cerebral anomalies); **ERG** for retinal dystrophy (uniformly abnormal) (PMID: 37225827).
- **Immunology:** Immunoglobulin levels and lymphocyte/B-cell subset quantification (PMID: 38837402).
- **CMA/karyotype:** Characteristically normal (do not detect *RNU4ATAC* point variants).
- **Differential diagnosis:** Other multiple epiphyseal dysplasias; other primordial dwarfisms, importantly **PCNT-related MOPD II** (distinguished by aneurysm/Moyamoya risk, PMID: 37234811); and within-gene RS/MOPD1.

11. Outcome / Prognosis

- **Survival:** In LWS (mild end) life expectancy is relatively preserved; the severe MOPD1 end is frequently lethal in infancy/early childhood. No LWS-specific mortality statistics exist.
- **Morbidity:** Driven by short stature/skeletal limitation, progressive visual impairment, cognitive impairment, and infection susceptibility.
- **Prognostic factors:** Variant position and allele combination (severity gradient); degree of immune deficiency (infection risk) and retinal dystrophy (visual prognosis).
- **Complications:** Recurrent infections (immune deficiency), progressive visual loss; non-ischemic cardiomyopathy reported at the RS end (PMID: 37666272).

12. Treatment

No disease-modifying or curative therapy exists; management is **supportive and multidisciplinary**: - **Immunoglobulin replacement / infection prophylaxis** for antibody deficiency (NCIT: Immunoglobulin Therapy). - **Ophthalmologic surveillance and low-vision support** for retinal dystrophy/nystagmus. - **Orthopedic/skeletal management and physical therapy** for epiphyseal dysplasia/short stature. - **Developmental/educational support** for delay/intellectual disability. - **Dermatologic management** of chilblain-like lesions (type I interferon involvement suggests a theoretical rationale for immunomodulation, but this is investigational). - **Experimental:** No approved gene/RNA therapies; the minor-intron-retention readout could in principle serve as a pharmacodynamic biomarker for future splice-modulating approaches. No registered disease-specific clinical trials identified.

13. Prevention

- **Genetic counseling** for 25% recurrence risk; carrier testing of at-risk relatives (cascade testing).
- **Prenatal diagnosis / preimplantation genetic testing** feasible once familial variants are known — prenatal diagnosis has been reported for a subsequent pregnancy in an affected family (PMID: 29370840).
- **Tertiary prevention:** infection prophylaxis, vision monitoring, developmental intervention.
- No primary prevention (not environmentally modifiable); not vaccine-preventable.

14. Other Species / Natural Disease

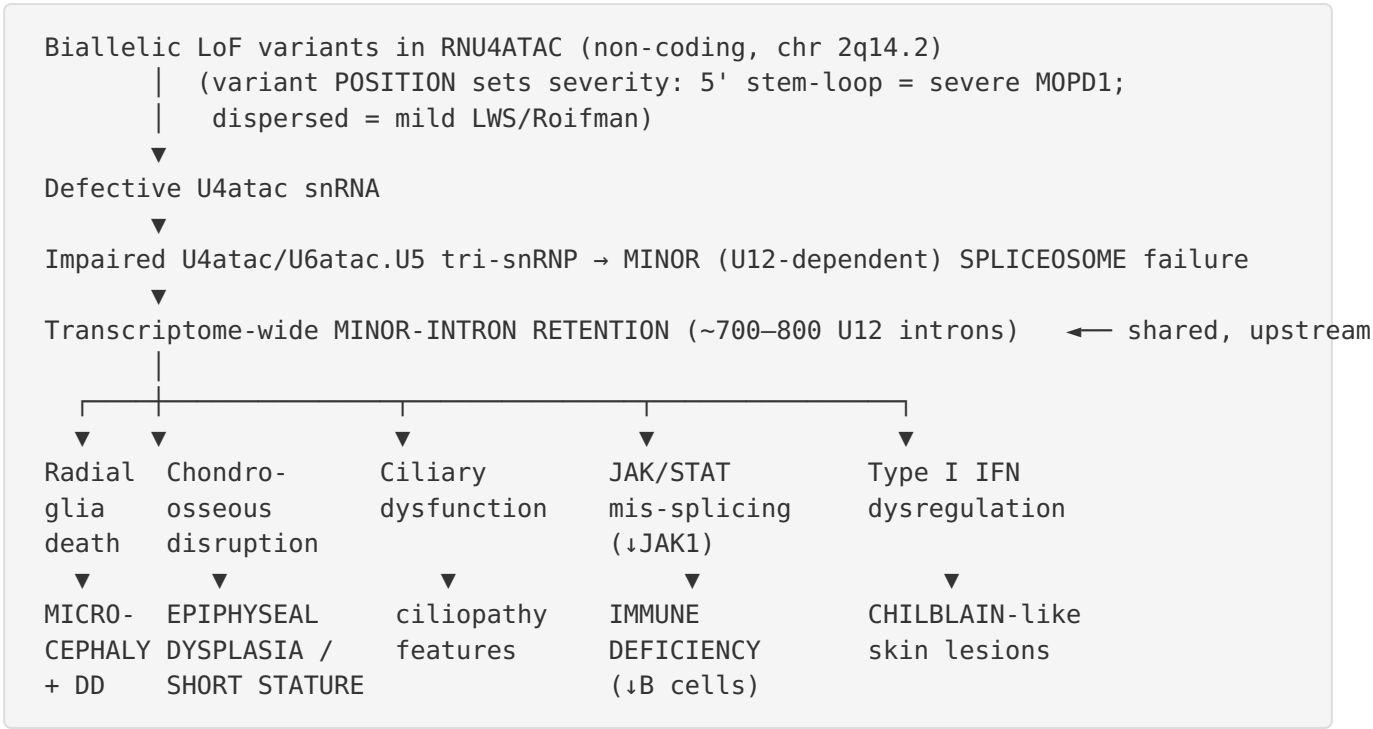
- No naturally occurring companion-animal/wildlife disease ortholog is catalogued (no OMIA entry for LWS specifically).
- *RNU4ATAC*/minor-spliceosome components are **deeply evolutionarily conserved** (present from *Drosophila* to mammals), enabling cross-species modeling. Orthologous minor-spliceosome snRNA function is conserved in mouse and zebrafish.
- No zoonotic potential (non-infectious genetic disorder).

15. Model Organisms

Model	Manipulation	Phenotype recapitulated	PMID
Mouse (cortex)	Conditional Rnu11 (U11) ablation	Microcephaly via radial glial cell-cycle defects/death	30093551
Mouse (limb)	U11 snRNA loss	Micromelia (limb skeletal dysplasia)	32665241
Drosophila	CRISPR U4atac stem-II mutant	Growth/neurodevelopmental defects, immunodeficiency, GI symptoms; JAK/STAT mis-splicing	42463491
Zebrafish	U4atac knockdown	Ciliary defects	36802443
Human patient cells	Native biallelic variants + reporter assay	Minor-intron retention (direct molecular phenotype)	26522830, 32628740

Strengths: Mouse models directly link minor-spliceosome loss to microcephaly and skeletal dysplasia; *Drosophila* captures the immune axis. **Limitations:** Most models ablate *U11/Rnu11* (a different minor-spliceosome snRNA) rather than *RNU4ATAC* itself, and complete ablation is more severe than the hypomorphic human variants; no model specifically reproduces the mild LWS end of the spectrum.

Mechanistic Model / Interpretation



The model's central logic is that a **single upstream lesion (minor-intron retention)** produces a **pleiotropic, multisystem phenotype** because minor introns reside in functionally diverse genes. The **severity gradient** (LWS ↔ RS ↔ MOPD1) is explained quantitatively by how much a given variant degrades tri-snRNP assembly (FitCons-weighted, position-dependent). Tissue selectivity (why brain, skeleton, retina, and immune cells are preferentially affected) likely reflects the high proliferative/biosynthetic demand of neural and chondro-osseous progenitors and the splicing dependence of key cell-cycle and signaling transcripts.

Evidence Base

PMID	Study (abbrev.)	Role
29265708	Expanding phenotype of RNU4ATAC to LWS	**Establishes** biallelic RNU4ATAC as cause of LWS
30368667	LWS: RNU4ATAC association, genotype–phenotype	**Supports** severity-by-variant-position; defines phenotype
41808109	Phenotypic spectrum: 4 novel + reeval	**Supports** MOPD1→RS severity spectrum
42322193	RNU4ATAC-opathy large cohort (n=60)	**Supports** core features, minor-intron retention, RNA-seq reclassification
36622817	Delineating RNU4ATAC spliceosomopathy	**Supports** continuum (one patient spanning all three)
26522830	Roifman syndrome, minor intron splicing	**Supports** U4atac essential; minor-intron defect mechanism
32628740	Clinical interpretation of RNU4ATAC variants	**Supports** non-coding diagnostic challenge; reporter assay
30093551	Minor spliceosome inactivation → microcephaly	**Supports** microcephaly mechanism (mouse)
32665241	U11 loss → micromelia	**Supports** skeletal mechanism (mouse)
36802443	U4atac deficiency → ciliary defects	**Supports** ciliary branch
42463491	U4atac regulates JAK/STAT (Drosophila)	**Supports** immune/JAK-STAT branch
40415209	RNU4ATAC chilblain lesions, type I IFN	**Supports** interferon/skin branch
37225827	Retinal dystrophy in RNU4ATAC-Roifman	**Supports** rod-cone dystrophy phenotype
38837402	B-cell deficiency in MOPD1 twins	**Supports** immunodeficiency across spectrum
3706411	Nevin 1986, LWS second family	**Supports** historical description, AR inheritance
29370840	Chinese family, WES-negative, targeted RNU4ATAC	**Supports** diagnostic pitfalls, prenatal diagnosis

PMID	Study (abbrev.)	Role
37666272	Roifman as non-ischemic cardiomyopathy	**Supports** exome-kit coverage gap; phenotypic breadth
37234811	PCNT MOPD II with aneurysm/ Moyamoya	**Differential**: PCNT-MOPD II is distinct from RNU4ATAC disorders

Evidence spans **human clinical/genetic** (majority), **in vitro functional** (reporter assay, patient RNA-seq), and **model organism** (mouse, zebrafish, *Drosophila*) sources, providing convergent support for the minor-intron-retention mechanism.

Limitations and Knowledge Gaps

1. **No LWS-specific epidemiology.** Prevalence, incidence, carrier frequency, and sex/age distributions are unquantified given extreme rarity; most data are pooled across the RNU4ATAC-opathy spectrum.
2. **Genotype–phenotype resolution is incomplete.** The FitCons/position model explains broad severity trends but cannot yet reliably predict LWS vs RS vs MOPD1 for a novel allele combination.
3. **Model limitations.** Most animal models ablate *U11/Rnu11* rather than *RNU4ATAC*, and use complete knockouts rather than hypomorphic alleles; no model specifically phenocopies the mild LWS end.
4. **Tissue-selectivity unexplained.** Why specific tissues (brain, skeleton, retina, B cells) are preferentially vulnerable despite a housekeeping defect remains mechanistically unresolved.
5. **Secondary pathways (cilia, JAK/STAT, IFN)** are derived partly from allelic disorders/model organisms; their contribution specifically in mild LWS is inferred, not directly demonstrated.
6. **No natural-history or QoL data**, and no therapeutic trials — management recommendations are extrapolated from case experience.

Proposed Follow-up Experiments / Actions

1. **Establish a prospective RNU4ATAC-opathy registry** capturing genotype, minor-intron-retention burden (RNA-seq), and longitudinal phenotype (growth, vision/ERG, immune function, neurodevelopment) to quantify natural history and refine genotype–phenotype prediction.
2. **Build hypomorphic, allele-specific models** (knock-in of human LWS vs MOPD1 variants in *RNU4ATAC* itself; mouse and/or patient iPSC-derived cerebral and chondro-osseous organoids) to directly test the position-severity model and tissue selectivity.
3. **Standardize a quantitative minor-intron-retention assay** as a clinical functional test to resolve VUS and correlate retention burden with severity (candidate severity biomarker).
4. **Targeted-sequencing / WGS reflex testing** in any microcephalic-primordial-dwarfism or multiple-epiphyseal-dysplasia patient with negative exome — raise diagnostic yield by ensuring *RNU4ATAC* coverage.
5. **Pathway-directed therapeutic exploration:** test whether modulating type I interferon or JAK/STAT signaling ameliorates immune/skin phenotypes, and evaluate splice-modulating small molecules/ASOs using minor-intron-retention as a pharmacodynamic endpoint.
6. **Systematic immunologic and ophthalmologic surveillance protocols** for diagnosed patients, given the demonstrated antibody deficiency and progressive rod-cone dystrophy.

Report compiled from 24 primary references spanning human clinical, in vitro functional, and model-organism evidence. Causal gene: RNU4ATAC (U4atac snRNA, minor spliceosome). Disease: Lowry-Wood syndrome, MONDO:0009191.
