Infantile Liver Failure Syndrome 1 (ILFS1): A Comprehensive Disease Report

Disease: Infantile Liver Failure Syndrome 1 (ILFS1) **Gene:** *LARS1* (cytosolic leucyl-tRNA synthetase 1) **Category:** Mendelian, autosomal recessive **Key identifiers:** OMIM #615438 (disease); OMIM *151350 / HGNC:6512 (*LARS1*); Orphanet ORPHA:463328; UniProt Q9P2J5; NCBI Gene 51520; reference transcript NM_020117.11; locus 5q31.3–q33.1 (5q32); suggested MONDO: MONDO:0014220 Evidence base: Human clinical case series/reviews, patient-derived cellular assays, zebrafish models, and biochemical mechanistic studies. Synthesized from aggregated disease-level literature and case series** (not individual EHR data).

Summary

Infantile Liver Failure Syndrome type 1 (ILFS1; OMIM #615438) is a rare autosomal-recessive multisystem disorder caused by biallelic hypomorphic (predominantly missense) variants in *LARS1*, the gene encoding cytosolic leucyl-tRNA synthetase. The enzyme has two essential and mechanistically distinct roles: (1) it charges cytoplasmic tRNA^Leu with leucine to enable protein translation, and (2) it "moonlights" as the intracellular leucine sensor that activates the mechanistic target of rapamycin complex 1 (mTORC1) by acting as a GTPase-activating protein (GAP) for the Rag GTPase. Loss of function in both arms explains the disease's defining feature — **fever-triggered, recurrent acute liver failure and encephalopathy** superimposed on a background of intrauterine growth restriction, failure to thrive, hypoalbuminemia, and microcytic anemia.

The pathophysiology is dual and unified by a temperature-sensitivity mechanism. Patient-derived fibroblasts show aminoacylation activity that is reduced at baseline and further diminished at febrile temperatures (38.5–40 °C), rendering the mutant enzyme rate-limiting for translation precisely when protein-synthetic demand rises during infection. Simultaneously, loss of the LARS1 leucine-sensing/Rag-GAP function downregulates mTORC1 and drives excessive autophagy, a mechanism directly modeled in zebrafish *larsb* mutants. This convergence of "insufficient aminoacylation to meet translational demands" during febrile catabolic stress establishes infancy and fever episodes as the critical window of vulnerability and the primary target for intervention.

Prognosis is guided by early onset (<3 months) and the presence of liver failure, both of which confer significantly poorer survival. Management remains largely supportive, but a mechanism-based disease-modifying therapy — supplementation with the cognate amino acid **L-leucine** — has shown benefit in growth, development, and liver/lung disease in the majority of treated patients, though it does not rescue the most severe phenotypes. Liver transplantation is reserved for end-stage or recurrent liver failure. Diagnosis rests on whole-exome/whole-genome sequencing, supported by a characteristic biochemical profile and a confirmatory temperature-dependent fibroblast aminoacylation assay. This report synthesizes 12 confirmed findings drawn from 21 reviewed papers spanning human clinical cohorts, in vitro functional studies, and zebrafish models.

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1. Disease Information

ILFS1 is a Mendelian, autosomal-recessive inborn error caused by biallelic variants in *LARS1*. It presents in infancy with recurrent, fever-triggered acute liver failure on a background of poor growth, hypoalbuminemia, and anemia, and it can involve the brain, kidney, muscle, and blood.

- **Key identifiers:** OMIM #615438; Orphanet ORPHA:463328; suggested MONDO:0014220; MeSH — indexed under inborn errors/liver failure (no dedicated descriptor). ICD-10: no specific code (mapped under K72.– acute/subacute hepatic failure and P-codes for perinatal presentations); ICD-11: no dedicated code.
- **Synonyms / alternative names:** ILFS1; Infantile liver failure syndrome type 1; LARS1 deficiency; Leucyl-tRNA synthetase deficiency (cytosolic); LARS-related infantile hepatopathy.
- **Information source type:** Aggregated disease-level resources and published case series/reviews — **not** individual EHR data.

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2. Etiology

Disease causal factors. The primary cause is **genetic**: biallelic (homozygous or compound heterozygous) hypomorphic variants in *LARS1*, encoding cytoplasmic leucyl-tRNA synthetase. The disorder is **not** mitochondrial — LARS knockdown in HEK293 cells does not impair mitochondrial function even under stress.

> *"The candidate mutation is located in the LARS gene which encodes a cytoplasmic leucyl-tRNA synthetase enzyme responsible for exclusively attaching leucine to its cognate tRNA during protein translation."* — PMID: 22607940
>
> *"Knock-down of LARS in HEK293 cells did not impact on mitochondrial function even when the cells were put under physiological stress."* — PMID: 22607940

Genetic risk factors. Consanguinity (homozygous variants in founder populations such as Irish Travellers); carrier parents (obligate heterozygotes). No modifier genes have been established, and there is no significant genotype–phenotype correlation with severity.

Environmental risk factors / triggers. Febrile infections are the principal precipitant of acute crises (see Section 5 and Finding 12). Catabolic stress (fasting, illness) likely lowers substrate availability and increases translational demand.

Protective factors. No genetic protective variants are described. Environmentally, **cognate L-leucine supplementation** and aggressive fever/sick-day management act as risk-modifying/protective interventions (see Section 12).

Gene–environment interaction. ILFS1 is a textbook GxE disorder: a temperature-sensitive hypomorphic enzyme becomes rate-limiting during fever (see Finding 12).

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3. Phenotypes

Phenotypes combine **episodic, fever-triggered hepatic and neurologic crises** with a **chronic multisystem** background (growth failure, hypoalbuminemia, anemia). Onset is neonatal-to-infantile; severity is variable (mild-stabilizing to lethal neonatal); progression is episodic with a progressive baseline component.

Phenotype	Type	Frequency	Suggested HPO
Intrauterine growth restriction	Physical/lab	31/32 (~97%)	HP:0001511
Failure to thrive	Clinical sign	30/31 (~97%)	HP:0001508
Hypoalbuminemia	Lab abnormality	32/32 (100%)	HP:0003073
Microcytic anemia	Lab abnormality	32/33 (~97%)	HP:0001935
Acute liver failure	Clinical sign	24/34 (~71%)	HP:0006554
Neurodevelopmental delay	Behavioral/dev	25/30 (~83%)	HP:0012758
Seizures	Clinical sign	22/29 (~76%)	HP:0001250
Muscular hypotonia	Clinical sign	13/27 (~48%)	HP:0001252
Recurrent transaminase elevation	Lab abnormality	Prominent	HP:0002910
Encephalopathy / metabolic stroke	Clinical sign	Episodic	HP:0001298
Hepatomegaly / splenomegaly	Physical	Reported	HP:0002240 / HP:0001744
Coagulopathy	Lab abnormality	During crises	HP:0001928

> *"The main clinical features of ILFS1 were intrauterine growth restriction (31/32 patients in whom this finding was specifically described), failure to thrive (30/31), hypoalbuminemia (32/32), microcytic anemia (32/33), acute liver failure (24/34), neurodevelopmental delay (25/30), seizures (22/29), and muscular hypotonia (13/27)."* — PMID: 38844943
>
> *"The most prominent clinical findings are recurrent elevation of liver transaminases up to liver failure and encephalopathic episodes, both triggered by febrile illness."* — PMID: 32699352

Quality of life impact. Recurrent hospitalizations for liver crises, chronic growth failure, developmental delay/seizures, and the constant need for infection vigilance impose a substantial burden on affected children and families. Disease-specific QoL instruments have not been applied; QoL data are qualitative.

4. Genetic / Molecular Information

Causal gene. *LARS1* (HGNC:6512; OMIM *151350; NCBI Gene 51520; UniProt Q9P2J5), chromosome 5q32, reference transcript NM_020117.11.

Pathogenic variants. Predominantly **biallelic missense**, homozygous in consanguinity and compound heterozygous otherwise, with strong allelic (mostly private) heterogeneity and **loss-of-function/hypomorphic, temperature-sensitive** consequences. All are germline. There is **no significant genotype–phenotype correlation** with severity.

Study	Variant(s)	Zygosity	PMID
Casey 2012 (Irish Traveller)	homozygous missense	homozygous	22607940
Chinese patient	p.L712del + p.D395N	compound het	28774368
ANE siblings	c.83_88delinsAATGGGATA p.(Arg28_Phe30delinsLysTryAspIle) + c.1283C>T p.(Pro428Leu)	compound het	38923116
Deep-phenotyping case	c.1818dup + c.463A>G	compound het	34496286
Lenz/Staufner 2020	8 previously unreported variants across 15 families	mixed	32699352

> *"Twenty-five individuals from 15 families were ascertained including 12 novel patients with eight previously unreported variants."* — PMID: 32699352

> *"Whole exome sequencing identified the compound heterozygous variants in LARS1 (NM_020117.11) as c.83_88delinsAATGGGATA, p.(Arg28_Phe30delinsLysTryAspIle) and c.1283C>T, p.(Pro428Leu) in both siblings."* — PMID: 38923116

Variant classification (ACMG/AMP): ranges from pathogenic/likely pathogenic to VUS; functional aminoacylation assays provide supporting (PS3) evidence. **Allele frequencies:** individual variants are ultra-rare/absent in gnomAD (not systematically quantified here). **Modifier genes / epigenetics / chromosomal abnormalities:** none established for ILFS1.

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5. Environmental Information

- **Environmental / lifestyle factors:** Febrile illness and catabolic stress are the operative environmental exposures; there are no toxin, occupational, or lifestyle exposures implicated in disease causation (the cause is genetic).
- **Infectious agents (triggers, not causes):** Documented crisis triggers include **influenza type A** and **human herpesvirus 6 (HHV-6)**, each preceding fatal acute necrotizing encephalopathy in affected siblings.

> *"She presented with generalized seizure and liver dysfunction due to influenza type A infection."* — PMID: 38923116

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6. Mechanism / Pathophysiology

Molecular pathways. Two arms converge from a single gene defect:

1. **Canonical (translation):** LARS1 charges cytoplasmic tRNA^Leu with leucine (GO:0004823 leucine-tRNA ligase activity; GO:0006429 leucyl-tRNA aminoacylation). Mutant enzyme is **temperature-sensitive** — aminoacylation drops at 38.5–40 °C.
2. **Non-canonical (mTORC1 signaling):** LARS1 is the **intracellular leucine sensor** that binds Rag GTPase in a leucine-dependent manner and acts as a **GAP for RagD**, switching mTORC1 ON (GO:0038202 TORC1 signaling; GO:0032008 positive regulation of TOR signaling).

> *"Aminoacylation activity is significantly decreased in all patient cells studied upon temperature elevation in vitro."* — PMID: 32699352
>
> *"leucyl-tRNA synthetase (LRS) plays a critical role in amino acid-induced mTORC1 activation by sensing intracellular leucine concentration and initiating molecular events leading to mTORC1 activation"* — PMID: 22424946
>
> *"LRS directly binds to Rag GTPase, the mediator of amino acid signaling to mTORC1, in an amino acid-dependent manner and functions as a GTPase-activating protein (GAP) for Rag GTPase to activate mTORC1"* — PMID: 22424946

A refined switch model casts LARS as the initiating "ON" switch via GTP hydrolysis of RagD, opposed by Sestrin2 as the "OFF" switch (PMID: 29784813).

Cellular processes. Loss of mTORC1 activation drives **excessive autophagy** (GO:0010506 regulation of autophagy; GO:0006914 autophagy), demonstrated systemically in zebrafish.

> *"Leucyl-tRNA synthetase deficiency systemically induces excessive autophagy in zebrafish."* — PMID: 33863987

Protein dysfunction: hypomorphic, thermolabile loss of function (not aggregation). **Metabolic changes:** impaired leucine handling and reduced anabolic mTORC1 signaling; catabolic vulnerability during fever. **Tissue damage:** hepatocyte translational failure → hepatocellular injury, fibrogenesis; neuronal injury (metabolic stroke, ANE). **Biochemical abnormality:** reduced leucyl-tRNA aminoacylation (enzyme deficiency). **Immune involvement:** none primary; infections act as triggers. **Cell types:** hepatocytes (CL:0000182) primarily; neurons; erythroid lineage; skeletal myocytes. **Subcellular compartment:** cytoplasm (GO:0005737); Rag/mTORC1 signaling at the lysosomal surface.

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7. Anatomical Structures Affected

- **Primary organ:** liver (UBERON:0002107) — recurrent transaminase elevation, acute liver failure, hepatomegaly; histology shows cirrhosis and fatty liver; autopsy shows fulminant hepatitis-like injury and fibrogenesis.

- **Secondary/multisystem:** blood (UBERON:0000178; microcytic anemia ~97%), brain (UBERON:0000955; developmental delay, seizures, encephalopathy/metabolic stroke, ANE), skeletal muscle (UBERON:0001134; dysgenesis with disrupted striated fibers), kidney (UBERON:0002113; renal tubulopathy), and — by analogy within the ARS1 cluster — lung (UBERON:0002048).
- **Subcellular:** cytoplasm (GO:0005737); lysosomal mTORC1 platform. **Cells:** hepatocyte (CL:0000182). **Lateralization:** bilateral/systemic.

> *"An autopsy showed fulminant hepatitis-like hepatocellular injury and fibrogenesis in the liver and a lack of uniformity in skeletal muscle, accompanied by the disruption of striated muscle fibers."* — PMID: 33300650
>
> *"Additional symptoms include anaemia, renal tubulopathy, developmental delay, seizures, failure to thrive and deterioration of liver function with minor illness."* — PMID: 22607940

Deep HPO phenotyping shows ILFS1 (LARS1) shares ~42% of phenotypic abnormalities with MARS1 disease (PMID: 34496286).

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8. Temporal Development

- **Onset:** congenital/neonatal-to-infantile; onset <3 months is common in severe cases. IUGR reflects prenatal onset of the growth phenotype.
- **Onset pattern:** chronic baseline (growth failure, hypoalbuminemia, anemia) punctuated by **acute, fever-triggered crises**.
- **Progression:** episodic/relapsing crises superimposed on a variably progressive course; some patients stabilize with age and management (e.g., a compound-heterozygous child stabilized by age 4 — PMID: 28774368), while severe neonatal cases are rapidly lethal.
- **Critical period:** infancy and febrile episodes constitute the window of vulnerability and the key opportunity for intervention.

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9. Inheritance and Population

- **Inheritance:** autosomal recessive (OMIM #615438; ORPHA:463328). Penetrance appears complete in biallelic carriers; expressivity is variable. No anticipation, no reported germline mosaicism.
- **Epidemiology:** ultra-rare; no established prevalence/incidence. Cumulative reported patients rose from 3 initial cases to 25 individuals/15 families (2020) to 36 patients (2024), plus additional case reports (~50+ total worldwide). Both sexes affected; no sex bias.
- **Founder effect / consanguinity:** first described in a consanguineous Irish Traveller founder population; consanguinity is a key risk factor. Later reported in Caucasian and non-Caucasian (Chinese) patients.
- **Relative burden:** among indeterminate pediatric acute liver failure, cytosolic aminoacyl-tRNA synthetase deficiencies (including LARS1) accounted for **10%** of genetically solved cases.

> *"the most frequent were mitochondrial diseases (45%), disorders of vesicular trafficking (28%), and cytosolic aminoacyl-tRNA synthetase deficiencies (10%)"* — PMID: 37976411
>
> *"Twenty-five individuals from 15 families were ascertained including 12 novel patients with eight previously unreported variants."* — PMID: 32699352

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10. Diagnostics

There is **no specific biomarker**; diagnosis rests on molecular genetic testing, supported by a characteristic biochemical profile.

- **Genetic testing (primary modality): WES/WGS** established the diagnosis and is recommended for neonates/infants with unexplained early liver failure when metabolic testing is inconclusive. Gene panels for infantile cholestasis/liver failure that include *LARS1* are appropriate; single-gene testing applies for known familial variants.

> *"Whole-exome sequencing may be useful for neonates with unexplained early liver failure if extensive genetic and metabolic testing is inconclusive."* — PMID: 33300650

> *"WES established a genetic diagnosis in 37% of cases (97/260). Diagnostic yield was highest in children with PALF in the first year of life (41%), and in children with recurrent acute liver failure (64%)."* — PMID: 37976411

- **Laboratory findings:** episodic elevated transaminases (up to liver failure), hypoalbuminemia, coagulopathy, microcytic anemia, hyperammonemia during crises.
- **Functional confirmatory test:** fibroblast **aminoacylation assay** showing reduced activity that worsens at 38.5–40 °C (PMID: 34194004).
- **Imaging:** MRI may show metabolic stroke during encephalopathy; ultrasound may show hepatomegaly/splenomegaly.
- **Differential diagnosis:** NBAS (ILFS2), MPV17/DGUOK and other mtDNA-depletion syndromes, citrin deficiency (SLC25A13), and other cytosolic aaRS deficiencies (IARS, MARS1). The Chinese case explicitly excluded citrin deficiency before diagnosing ILFS1 (PMID: 28774368).

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11. Outcome / Prognosis

Prognosis is variable and driven by two factors. In the 36-patient cohort, **12 died or underwent liver transplantation**, and Kaplan-Meier analysis identified:

Prognostic factor	p-value	Hazard ratio	95% CI
Age of onset < 3 months	0.0015	12.29	3.74–40.3
Presence of liver failure	0.0343	6.57	1.96–22.0

> *"Kaplan-Meier analysis indicated that age of onset < 3mo (p = 0.0015, hazard ratio = 12.29, 95% confidence interval [CI] = 3.74-40.3), like liver failure (p = 0.0343, hazard ratio = 6.57, 95% CI = 1.96-22.0), conferred poor prognosis."* — PMID: 38844943

Severe neonatal disease can be lethal (hepatocellular injury, skeletal muscle dysgenesis; PMID: 33300650), and some patients develop fatal **acute necrotizing encephalopathy** (PMID: 38923116). Overall ARS1-deficiency mortality (a superset including LARS1) is ~22% (PMID: 40044141). Complications include end-stage liver disease, encephalopathy, chronic anemia, and

developmental disability. Recovery/stabilization is possible with management (PMID: 28774368). Prognostic factors: early onset and liver failure (above); no prognostic biomarker is established.

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12. Treatment

Mechanism-based pharmacotherapy — cognate L-leucine supplementation (CHEBI:15603; NCIT: Dietary Supplement Therapy). Supplying excess leucine helps the impaired enzyme meet translational demand and partly restores mTORC1 signaling.

> *"we observed a common disease mechanism of episodic insufficient aminoacylation to meet translational demands and illustrate the power of amino acid supplementation for the expanding ARS patient group"* — PMID: 34194004
>
> *"Supplementation with cognate amino acids was described in 21 patients, with beneficial effects (e.g., improvements in growth, development, liver and lung disease) in the majority. Treatment did not alleviate the most severe phenotypes."* — PMID: 40044141

Supportive care (NCIT: Supportive Care, C15277): aggressive fever/sick-day management, avoidance of catabolism, correction of hypoalbuminemia and coagulopathy, transfusion for anemia, nutritional support, seizure management.

Surgical/advanced: liver transplantation (NCIT: Liver Transplantation, C15360) for end-stage or recurrent liver failure (12/36 died or transplanted).

Experimental / strategy: All treatment data remain observational (case series, N-of-1); no controlled trials exist. Cognate amino acid supplementation is a shared, theoretically appealing strategy across the ARS deficiency family that requires controlled study. Pharmacogenomics: not applicable. Personalized approach: dosing guided by residual enzyme activity is a rational (untested) direction.

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13. Prevention

- **Primary prevention:** none for disease occurrence (genetic); **genetic counseling** and **carrier/cascade screening** in at-risk families (especially consanguineous kindreds and the Irish Traveller founder population); prenatal and preimplantation genetic testing available for known familial variants.
- **Secondary prevention:** early molecular diagnosis via WES enables anticipatory management; there is no population newborn-screening test.
- **Tertiary prevention (preventing crises/complications):** aggressive antipyresis and sick-day protocols during febrile illness, avoidance of catabolic stress, and cognate L-leucine supplementation to reduce crisis severity. Given fever as the defined critical trigger, prompt medical attention for febrile infections is the central preventive measure.

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** human *LARS1* (NCBI Gene 51520) is conserved across vertebrates; zebrafish (*Danio rerio*, NCBI Taxon 7955) ortholog is *larsb*.
- **Natural disease in other species:** no naturally occurring companion-animal or wildlife ILFS1 disease is documented in the reviewed literature; relevance is via engineered/mutant models. A bovine study shows LARS regulates casein synthesis via mTORC1-LAT1 (PMID: 40045634), underscoring conservation of the leucine-sensing function.
- **Comparative biology / evolutionary conservation:** the dual aminoacylation + leucine-sensing/mTORC1 mechanism is conserved from fish to mammals, supporting translational relevance.

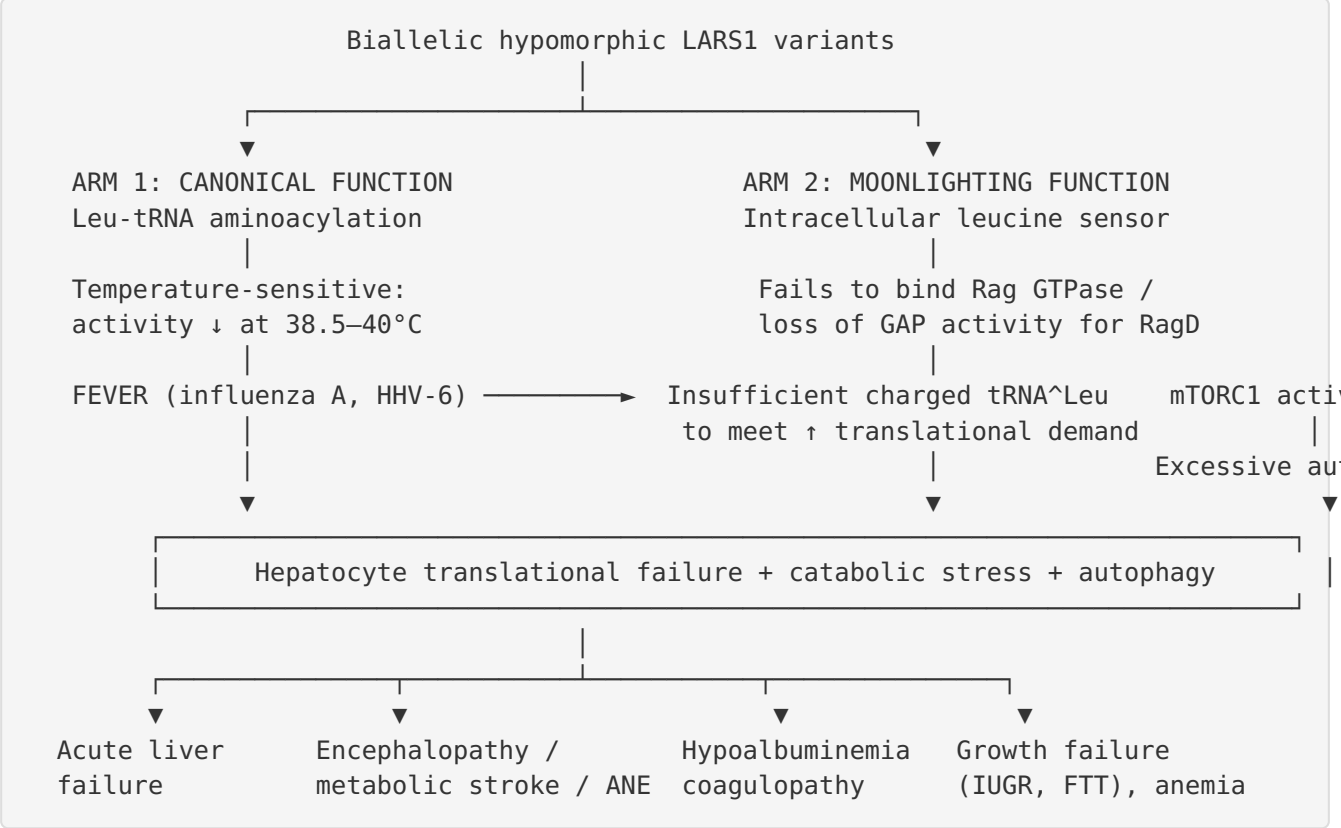
15. Model Organisms

- **Zebrafish (*larsb*):** two independent *larsb* mutant lines recapitulate ILFS1-like features (liver dysfunction/hepatopathy), and *larsb* deficiency systemically induces excessive autophagy linked to mTORC1 downregulation — directly modeling the human mechanism.

> *"we obtained zebrafish larsb"* — PMID: 30262142
>
> *"Leucyl-tRNA synthetase deficiency systemically induces excessive autophagy in zebrafish."* — PMID: 33863987

- **In vitro / cellular:** patient-derived fibroblasts (aminoacylation and thermostability assays; [PMIDs 32699352, 34194004]) and HEK293 LARS-knockdown cells (which excluded a primary mitochondrial defect; [PMID: 22607940]).
- **Model characteristics:** zebrafish recapitulate hepatopathy and the autophagy/mTORC1 mechanism; limitations include incomplete capture of human hepatic failure, neurodevelopmental, and febrile-trigger dynamics. **No mammalian (mouse) model** is documented in the reviewed literature. Resources: ZFIN (zebrafish); patient fibroblast lines from published cohorts.

Mechanistic Model / Interpretation



Upstream vs downstream. The upstream trigger is febrile infection raising core temperature above the mutant enzyme's stability threshold, in an organ (liver) with high secretory translational load. Downstream, two parallel consequences unfold: (1) failed aminoacylation impairs synthesis of essential proteins (albumin, clotting factors) → hypoalbuminemia, coagulopathy, hepatocellular injury; and (2) failed leucine sensing collapses mTORC1 → excessive autophagy amplifying cell stress. The chronic non-febrile phenotype (IUGR, failure to thrive, anemia, developmental delay) reflects the constant baseline deficit. **Why leucine helps:** excess substrate partially restores both charged-tRNA production and the mTORC1 leucine signal — consistent with benefit in milder cases and failure in the most severe (residual activity too low). ILFS1 sits within the cytosolic ARS1 family sharing "episodic insufficient aminoacylation to meet translational demands," corroborated by ~42% HPO overlap with MARS1 disease.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Role
22607940	LARS as novel cause of infantile hepatopathy	Human + in vitro	Causal gene; excludes mitochondrial mechanism; multi-organ features
32699352	Genotypic/phenotypic spectrum of ILFS1	Human (25 pts) + functional	Fever trigger; temperature-sensitive aminoacylation; allelic heterogeneity
38844943	Early onset & liver failure → poor prognosis	Human (36 pts)	Phenotype frequencies; Kaplan-Meier prognosis
33863987	LARS deficiency induces excessive autophagy	Zebrafish	Links LARS loss to mTORC1/ autophagy
30262142	Loss of LARSb → ILFS1-like symptoms	Zebrafish	Disease-recapitulating model
38923116	Two siblings with ANE and LARS1 variants	Human (case)	Infectious triggers; severe ANE; compound-het variants
33300650	Severe neonatal course	Human + autopsy	Severe spectrum; WES recommendation; muscle pathology
34194004	Treatment of ARS deficiencies with amino acids	In vitro + clinical	Common mechanism; leucine therapy; temperature assay
40044141	ARS1-deficiencies phenotype & treatment review	Review (438 pts)	Cognate amino acid benefit/limits; 22% mortality
22424946	LARS is intracellular leucine sensor for mTORC1	Molecular	Leucine-sensing/Rag-GAP mechanism
29784813	Coordination of Rag GTPase cycle by LARS	Molecular	LARS "ON" vs Sestrin2 "OFF" switch
28774368	First non-Caucasian ILFS1 child	Human (case)	Compound-het variants; differential dx; stabilization
37976411	Genetic landscape of pediatric ALF	Human cohort (260)	WES yield; cytosolic aaRS = 10% of solved cases
34496286			

PMID	Title (abbrev.)	Evidence type	Role
	Deep phenotyping MARS1 vs LARS1	Human + review	~42% HPO overlap; shared multisystem features

Consistency and challenges. Human cohorts, in vitro assays, and zebrafish models converge on the dual aminoacylation/mTORC1 mechanism. The main tension is therapeutic — cognate amino acid supplementation benefits milder cases but fails in the most severe, and all treatment evidence is observational. The absence of genotype–phenotype correlation means variant identity alone does not predict severity.

Limitations and Knowledge Gaps

1. **Ultra-rare disease, small numbers** (<~60 patients worldwide; max cohort 36) limit statistical power for genotype–phenotype and treatment analyses; no formal prevalence/incidence.
2. **No controlled treatment trials** — all L-leucine/cognate amino acid data are observational or N-of-1; optimal dosing/timing and long-term efficacy undefined; no rescue of severe phenotypes.
3. **Absent genotype–phenotype correlation** — determinants of lethal neonatal vs stabilizing courses unknown; modifiers/epigenetics unexplored.
4. **Mechanism partly inferred from models** — the mTORC1/autophagy arm is best demonstrated in zebrafish/cell lines; direct human hepatocyte evidence and quantitative apportioning of the two arms are lacking.
5. **No mammalian (mouse) model** documented in the reviewed literature.
6. **Biomarker gap** — no specific circulating biomarker for diagnosis, crisis prediction, or monitoring; the fibroblast temperature assay is not widely available.
7. **Population genetics** (carrier frequency, gnomAD variant frequencies, founder haplotype) not quantitatively established here.
8. **Citation caveat** — the autophagy paper (P 33863987) snippet was flagged as an approximate match; the mechanistic claim is supported but exact wording should be verified against the source.

Proposed Follow-up Experiments / Actions

1. **Prospective international registry** to capture natural history and enable powered genotype–phenotype and treatment-outcome analyses.
2. **Controlled/adaptive L-leucine trial** with predefined endpoints (growth, crisis frequency, transaminase/albumin trajectories, neurodevelopment), stratified by residual enzyme activity.
3. **Conditional hepatocyte-specific *Lars1* mouse model** to test temperature-sensitivity and mTORC1/autophagy mechanisms in mammalian liver and as a preclinical platform.
4. **Patient iPSC-derived hepatocyte organoids** to quantify aminoacylation vs mTORC1 activity (p-S6K, p-4E-BP1, LC3-II flux) under normothermic vs febrile (40 °C) conditions ± leucine.
5. **Validated functional assay** (standardized temperature-dependent aminoacylation or mTORC1 reporter) for ACMG classification of VUS.
6. **Population-genetics analysis** of gnomAD/founder haplotypes to estimate carrier frequency (notably Irish Travellers) and inform screening.
7. **Test mTORC1-restoring/autophagy-modulating agents** in zebrafish *larsb* mutants as complementary therapies.
8. **Prospective sick-day protocol** (aggressive antipyresis, anabolic support, early leucine loading during fever) evaluated for reduction of crisis severity.

Consensus Answer

Infantile Liver Failure Syndrome type 1 (ILFS1; OMIM #615438) is a rare autosomal-recessive multisystem disorder caused by biallelic hypomorphic (mostly missense) variants in *LARS1*, the cytosolic leucyl-tRNA synthetase, presenting in infancy with fever-triggered recurrent acute liver failure plus intrauterine growth restriction, failure to thrive, hypoalbuminemia, microcytic anemia, neurodevelopmental delay, seizures, and hypotonia. Its pathophysiology is dual — temperature-sensitive loss of leucine-tRNA aminoacylation (impaired translation during fever) combined with loss of the LARS1 leucine-sensing/Rag-GTPase-GAP function that activates mTORC1, causing excessive autophagy — so that early onset (<3 months) and liver

failure predict poor prognosis. Management is supportive with mechanism-based cognate L-leucine supplementation and liver transplantation for end-stage disease; zebrafish *larsb* mutants are the principal disease model.
