# Perlman Syndrome (DIS3L2): Comprehensive Disease Characteristics Report

**Disease:** Perlman Syndrome **MONDO ID:** MONDO:0009965 | **OMIM:** 267000 | **Orphanet:** ORPHA:2849 **Causal gene: DIS3L2** (DIS3-like 3′→5′ exoribonuclease 2; HGNC:28648; chromosome 2q37.1) **Inheritance:** Autosomal recessive **Category:** Mendelian

## Summary

Perlman syndrome is a rare, autosomal recessive congenital **overgrowth and Wilms tumor predisposition syndrome** caused by **biallelic loss-of-function variants in the *DIS3L2* gene** on chromosome 2q37.1. *DIS3L2* encodes a cytoplasmic 3′→5′ exoribonuclease of the RNase II/RNB (DIS3) family that specifically recognizes and degrades 3′-oligouridylated RNAs — most famously the uridylated precursors of the let-7 tumor-suppressor microRNA family, but also a broad spectrum of aberrant, highly structured non-coding RNAs. Loss of this RNA-surveillance activity is the initiating molecular lesion of the disease. The causal gene was identified by Astuti et al. in 2012, who mapped the locus to 2q37.1 and demonstrated germline *DIS3L2* mutations in affected individuals, along with somatic *DIS3L2* mutations in sporadic Wilms tumor [PMID: 22306653].

Clinically, Perlman syndrome presents prenatally and neonatally with **polyhydramnios, fetal macrosomia, a distinctive facial dysmorphism, nephromegaly, renal dysplasia with nephroblastomatosis, visceromegaly, facial hypotonia, and multiple congenital anomalies**. The prognosis is poor: most affected neonates die in infancy from respiratory and/or renal failure. Among the minority who survive the neonatal period, approximately **64% develop Wilms tumor and essentially all have developmental delay** [PMID: 18780370]. Because of this high renal cancer risk, Perlman syndrome is formally classified among the Wilms tumor predisposition syndromes, and affected survivors warrant intensive abdominal/

renal ultrasound surveillance (typically every ~3 months) per AACR and SIOP-Europe consensus guidelines [PMID: 39466169; 34134020].

Mechanistically, the disease is best understood as a failure of cytoplasmic RNA quality control. Biallelic *DIS3L2* loss removes oligo(U)-exoribonuclease activity, causing uridylated substrates (pre-let-7 and structured ncRNAs including 7SL/SRP RNA, RMRP, rRNA, tRNA, and snRNA) to accumulate. Downstream, proliferation is derepressed through activation of the **PI3K/AKT signaling pathway** (and AKT–GSK3β signaling), growth-factor dysregulation, and mitotic/spindle abnormalities — a cascade conserved from *Drosophila* to zebrafish to human cells [PMID: 33370287; 40500755; 22306653].

Notably, mature let-7 levels are unchanged in DIS3L2-deficient cells and mice, indicating that the tumor-suppressive mechanism is **largely let-7-independent** [PMID: 29950491]. This report integrates nine confirmed findings across the 15 requested domains and flags where evidence is scarce.

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## Key Findings

### Finding 1 — Perlman syndrome is an autosomal recessive overgrowth disorder caused by biallelic *DIS3L2* loss-of-function

Perlman syndrome results from **homozygous or compound heterozygous mutations in *DIS3L2*** (chromosome 2q37.1; OMIM 267000; MONDO:0009965). The *DIS3L2* gene product is a ribonuclease with homology to the DIS3 component of the RNA exosome. As stated in the Morris et al. review: *"Recently a Perlman syndrome locus was mapped to chromosome 2q37 and homozygous or compound heterozygous mutations were characterized in DIS3L2. The DIS3L2 gene product has ribonuclease activity and homology to the DIS3 component of the RNA exosome"* [PMID: 23613427].

The reported mutational spectrum includes **nonsense** (c.127C>T, p.Arg43Ter), **missense** (c.2381G>A, p.Arg794His), and **frameshift** variants (c.2109delC; c.1829_1830insC), as well as a recurrent **homozygous deletion of exon 9** generated by non-allelic homologous recombination (NAHR) between LINE-1 elements. Igarashi et al. documented this structural variant: *"We report the homozygous deletion of exon 9 of DIS3L2 in a Japanese patient with Perlman syndrome. We identified the deletion junction, and implicate a non-allelic homologous recombination (NAHR) between two LINE-1 (L1) elements as the causative mechanism"* [PMID: 23486540]. This has direct diagnostic importance: large exon-level deletions can be **missed by standard sequencing**, so copy-number-sensitive methods are required to avoid false-negative molecular diagnoses. A compound-heterozygous example (c.2109delC maternal; c.1829_1830insC paternal), classified pathogenic under ACMG criteria (PVS1+PS2+PM2), further enriches the known variant spectrum [PMID: 34964966].

## Finding 2 — DIS3L2 is the 3′→5′ exoribonuclease of the LIN28–TUT4/7–DIS3L2 pathway and a quality-control nuclease for uridylated/structured ncRNAs

DIS3L2 belongs to the **RNase II/RNB family** and is a DIS3 homolog, but — unlike DIS3 and DIS3L1 — it **lacks the PIN domain** and does **not** associate with the core RNA exosome, instead functioning as a free cytoplasmic enzyme. It specifically binds and degrades **3′-oligouridylated RNAs**. In the Lin28–let-7 axis, LIN28A/B recruit the terminal uridylyl transferases TUT4/7 to oligouridylate pre-let-7, which DIS3L2 then degrades. Chang et al. established DIS3L2 as the pathway's missing component: *"Here, we identify the Perlman syndrome-associated protein DIS3L2 as an oligo(U)-binding and processing exoribonuclease that specifically targets uridylated pre-let-7 in vivo. This study establishes DIS3L2 as the missing component of the LIN28-TUT4/7-DIS3L2 pathway required for the repression of let-7 in pluripotent cells"* [PMID: 24141620]. Independent biochemical/structural and cell-based work corroborates this role [PMID: 25119025;

P 26080928

].

P 23594738

The crystal structure of mouse Dis3l2 bound to oligoU RNA reveals **three RNA-binding domains forming an open funnel** with uracil-specificity interactions spanning the first ~12 nucleotides and three distinct "U-specificity zones" that explain substrate recognition [PMID: 25119025]. Beyond let-7, DIS3L2 performs **quality-control decay (Dis3l2-mediated decay, DMD)** of a wide range of aberrant structured ncRNAs: rRNAs, snRNAs, snoRNAs, tRNAs, 7SL, Y RNAs, the RMRP lncRNA, Pol III transcripts, and mRNAs. As Łabno et al. and Pirouz et al.

establish: *"This establishes Dis3l2-mediated decay (DMD) as a quality-control pathway that eliminates aberrant ncRNAs"* [PMID: 27498873], and the cytoplasmic DIS3L2-dependent "uridylome" encompasses a broad spectrum of highly structured, aberrantly processed RNAs [PMID: 27647875]. Critically, in DIS3L2-deficient cell lines and mouse models, **mature let-7 levels are unchanged**, demonstrating that *"DIS3L2 loss has no effect on mature let-7 levels"* [PMID: 29950491] — so tumor suppression is not simply mediated by let-7.

## Finding 3 — Clinical phenotype: fetal overgrowth with high neonatal mortality and Wilms tumor predisposition in survivors

The defining features of Perlman syndrome are **polyhydramnios, fetal macrosomia, characteristic facial dysmorphism, nephromegaly, renal dysplasia and nephroblastomatosis, facial hypotonia, and multiple congenital anomalies**. Most patients die in infancy from respiratory and/or renal failure; survivors have developmental delay and a high Wilms tumor risk. The *Three Siblings* case report notes: *"The majority of patients die in infancy due to respiratory and/or renal failure, limiting the reports of patients surviving into childhood"* [PMID: 40704758].

A **genotype–phenotype correlation** is emerging: the homozygous exon-9 deletion is associated with poor survival, while some missense or partial-function alleles (e.g., p.Arg794His) permit prolonged survival into childhood. A recent case report states: *"Survival is predicted by differences among various germline mutations in the DIS3L2 gene on chromosome 2q37.1, with prolonged survival documented in heterozygous mutations allowing partial exoribonuclease function"* [PMID: 42040973]. For Wilms tumor development, a **two-hit model** operates, combining a germline *DIS3L2* lesion with a somatic second hit: *"revealed 1 somatic mutation and 1 familial germline mutation in the DIS3L2 gene, suggesting a 2-hit causation of Wilms tumor"* [PMID: 35700413].

## Finding 4 — DIS3L2 loss drives overgrowth via PI3K/AKT activation and impaired RNA surveillance; recapitulated across model organisms

The proliferative mechanism is conserved and PI3K/AKT-dependent. In *Drosophila*, dis3L2-null and nuclease-dead lines show **catalytic-activity-dependent overproliferation** driven by the growth factor **Idgf2** (homolog of human chitinase-like CHI3L1/YKL-40); in human HEK-293T kidney cells, DIS3L2 loss increases proliferation and activates PI3-Kinase/AKT signaling. Towler et al. report: *"we show that loss of DIS3L2 results in an increase in the PI3-Kinase/AKT signalling pathway, which we subsequently show to contribute towards the proliferation phenotype"* [PMID: 33370287].

In **zebrafish**, dis3l2 morphants show neural crest apoptosis, mitotic/spindle defects, and Akt–GSK3β dysregulation: *"dis3l2 regulates neural tissue apoptosis and progenitor functions through the Akt-GSK3β signaling pathway"* [PMID: 40500755]. At the subcellular level, DIS3L2-mediated decay **safeguards 7SL/SRP-dependent ER-targeted translation and ER calcium homeostasis**; its loss causes sustained 7SL uridylation, calcium leak, and impaired stem-cell differentiation: *"Upon DIS3L2 loss, sustained 3'-end uridylation of aberrant 7SL RNA impacts ER-targeted translation and causes ER calcium leakage"* [PMID: 32457326].

## Finding 5 — Gene discovery: germline *DIS3L2* mutations cause Perlman syndrome; DIS3L2 regulates mitosis and cell growth and is mutated in sporadic Wilms tumor

The landmark gene-discovery paper (Astuti et al., 2012, *Nature Genetics*) mapped the Perlman locus and identified the causal gene: *"We mapped a previously unknown susceptibility locus to 2q37.1 and identified germline mutations in DIS3L2, a homolog of the Schizosaccharomyces pombe dis3 gene, in individuals with Perlman syndrome"* [PMID: 22306653]. The same study established DIS3L2's tumor-suppressor function and its relevance to sporadic (non-syndromic) Wilms tumor: *"DIS3L2 inactivation was associated with mitotic abnormalities and altered expression of mitotic checkpoint proteins. DIS3L2 overexpression suppressed the growth of human cancer cell lines, and knockdown enhanced the growth of these cells. We also detected evidence of DIS3L2 mutations in sporadic Wilms tumor"* [PMID: 22306653]. Thus DIS3L2 bridges a rare Mendelian overgrowth syndrome and common pediatric kidney cancer biology.

## Finding 6 — Perlman syndrome is a Wilms tumor predisposition syndrome warranting renal ultrasound surveillance

Perlman syndrome is classified among the Wilms tumor (WT) predisposition syndromes by consensus guidelines. The AACR Pediatric Cancer Working Group update notes: *"members of the AACR Pediatric Cancer Working Group met to update surveillance guidelines for patients with a predisposition to Wilms tumors with a review of recently published evidence and risk estimates"* [PMID: 39466169; P 39320341].

The SIOP-Europe Host Genome Working Group provides an independent consensus: *"the International Society of Pediatric Oncology (SIOP)-Europe Host Genome Working Group and*

*SIOP Renal Tumour Study Group hereby present updated WT surveillance guidelines"* [PMID: 34134020]. These groups recommend **abdominal/renal ultrasound surveillance (typically every ~3 months)** in children at increased WT risk.

Nephroblastomatosis/nephrogenic rests are the precursor lesions for Wilms tumor. Importantly, a large SIOP-WT-2001 analysis found that in **unilateral** Wilms tumor cohorts, the presence of nephrogenic rests did **not** independently worsen relapse-free or overall survival, indicating they are precursor markers rather than independent adverse prognostic factors once a tumor has formed [PMID: 42535789].

## Finding 7 — Prognosis quantified: high neonatal mortality; ~64% of neonatal survivors develop Wilms tumor and all have developmental delay

Alessandri et al. (2008) reviewed 28 reported Perlman syndrome patients and quantified the natural history. The prognosis is poor with high neonatal mortality: *"The prognosis of Perlman syndrome is poor with a high neonatal mortality rate"* [PMID: 18780370]. Among those surviving the neonatal period: *"Among the infants who survived beyond the neonatal period, 64% developed a WT and all had a developmental delay"* [PMID: 18780370]. Frequent manifestations include fetal macrosomia, ascites, polyhydramnios, nephromegaly, renal dysplasia, nephroblastomatosis, and distinctive facies.

Regarding inheritance in practice, reported sibships showed **parental consanguinity in only 2 of 7 families**: *"We review 19 patients from seven sibships with parental consanguinity in two families only"* [PMID: 18780370] — consistent with sporadic autosomal recessive occurrence rather than a requirement for consanguinity. **Cholestasis** has also been reported as a possibly novel feature [PMID: 20726997].

## Finding 8 — Clinical overlap with other overgrowth syndromes but molecular distinction from imprinting disorders

Perlman syndrome shares features (macrosomia, visceromegaly, Wilms tumor risk) with **Beckwith-Wiedemann syndrome** (BWS; 11p15 imprinting/CDKN1C) and **Simpson-Golabi-Behmel syndrome** (SGBS; GPC3), prompting frequent diagnostic confusion [PMID: 18780370; P 24215131 ; P 38161545 ].

*"Clinical overlaps with other overgrowth syndromes particularly Beckwith-Wiedemann syndrome and Simpson-Golabi-Behmel syndrome have been emphasized"* [PMID: 18780370].

However, in molecularly confirmed Perlman cases, the 11p15 region/CDKN1C and GPC3 were specifically excluded: *"Genetic or epigenetic alterations of the 11p15 region (involved in the BWS), including mutation of the CDKN1C gene were excluded. No mutation of the GPC3 gene was identified"* [PMID: 18780370]. This establishes Perlman as a **distinct autosomal recessive DIS3L2 disorder**, not an imprinting (BWS) or X-linked (SGBS) condition. Diagnosis therefore requires demonstration of **biallelic *DIS3L2* variants**, with care to detect large exon-9 deletions missed by sequencing [PMID: 23486540; 22306653].

## Finding 9 — Integrated causal chain: biallelic DIS3L2 loss → RNA-surveillance failure → PI3K/AKT-driven overgrowth and tumorigenesis (largely let-7-independent)

Synthesis of the mechanistic evidence defines the Perlman pathophysiology as a stepwise cascade (detailed in the Mechanistic Model below). The key integration points: (1) biallelic *DIS3L2* loss removes cytoplasmic 3′→5′ oligo(U)-exoribonuclease activity [PMID: 22306653; 25119025]; (2) uridylated substrates accumulate via failed DIS3L2-mediated decay [PMID: 24141620; 23594738; 27498873; 27647875; 32457326]; (3) proliferation is derepressed through elevated PI3K/AKT (and AKT-GSK3β) signaling and growth-factor dysregulation, with mitotic/spindle defects [PMID: 33370287; 40500755; 22306653]; (4) mature let-7 is unchanged, so tumor suppression is **largely let-7-independent** [PMID: 29950491]; (5) the pathway is conserved from *Drosophila* to humans [PMID: 33370287]. The clinical outcome is fetal overgrowth, nephroblastomatosis, and Wilms tumor (via two-hit somatic inactivation) [PMID: 35700413].

# Section-by-Section Report

## 1. Disease Information

Perlman syndrome (MONDO:0009965; OMIM 267000; Orphanet ORPHA:2849) is a **rare autosomal recessive congenital overgrowth syndrome with Wilms tumor predisposition**, caused by biallelic variants in **DIS3L2**. It was first described clinically by Perlman and colleagues as a familial syndrome of renal hamartomas, nephroblastomatosis, and fetal gigantism.

- **Key identifiers:** OMIM 267000; MONDO:0009965; Orphanet ORPHA:2849; causal gene DIS3L2 (HGNC:28648). MeSH does not maintain a dedicated descriptor; the condition is typically indexed under overgrowth syndromes / Wilms tumor predisposition. ICD-10 lacks a specific code (grouped under congenital malformation syndromes, e.g., Q87.3 overgrowth syndromes); ICD-11 similarly groups it under syndromic overgrowth.
- **Synonyms:** nephroblastomatosis–fetal ascites–macrosomia–Wilms tumor syndrome; renal hamartomas, nephroblastomatosis and fetal gigantism.
- **Information source:** Knowledge is derived almost entirely from **aggregated disease-level resources and small case series/case reports** (fewer than ~40 molecularly or clinically reported patients worldwide), not from large EHR cohorts.

## 2. Etiology

- **Disease causal factors:** Purely **genetic** — biallelic (homozygous or compound heterozygous) loss-of-function variants in *DIS3L2* [PMID: 22306653; P 23613427 ]. No environmental or infectious cause.
- **Genetic risk factors:** The causal variants themselves (nonsense, frameshift, missense, and the recurrent exon-9 deletion) are the risk determinants. Wilms tumor development additionally requires a **somatic second hit** at *DIS3L2* (two-hit model) [PMID: 35700413]. Somatic *DIS3L2* mutations also occur in sporadic Wilms tumor [PMID: 22306653].
- **Environmental risk factors:** None established. Consanguinity increases the chance of homozygosity but was present in only 2 of 7 reported sibships [PMID: 18780370].

- **Protective factors:** No genetic or environmental protective factors are documented. By inference, **residual exoribonuclease activity** from partial-function (e.g., missense p.Arg794His) alleles is associated with prolonged survival, functioning as a modifier of severity rather than a protective factor per se [PMID: 42040973].
- **Gene–environment interactions:** None documented; this is a highly penetrant Mendelian disorder.

## 3. Phenotypes

| Phenotype | Type | Onset | Frequency | Suggested HPO |
|---|---|---|---|---|
| Polyhydramnios | Prenatal sign | Fetal | Very frequent | HP:0001561 |
| Fetal macrosomia / overgrowth | Physical | Fetal/ neonatal | Very frequent | HP:0001520, HP:0000098 |
| Fetal ascites | Clinical sign | Fetal | Frequent | HP:0001791 |
| Nephromegaly | Physical | Neonatal | Very frequent | HP:0000105 |
| Renal dysplasia | Structural | Congenital | Frequent | HP:0000110 |
| Nephroblastomatosis / nephrogenic rests | Pathologic | Congenital | Characteristic precursor | HP:0001708 |
| Wilms tumor (nephroblastoma) | Neoplasm | Infancy/ childhood | ~64% of neonatal survivors | HP:0002667 |
| Distinctive facial dysmorphism | Physical | Congenital | Characteristic | HP:0001999 |
| Facial/generalized hypotonia | Neurologic | Neonatal | Frequent | HP:0000297 / HP:0001252 |
| Developmental delay / intellectual disability | Neurologic | Infancy | ~100% of survivors | HP:0001263 / HP:0001249 |
| Visceromegaly / organomegaly | Physical | Congenital | Frequent | HP:0003271 |
| Cholestasis | Lab/ clinical | Neonatal | Rare (reported) | HP:0001396 |

- **Severity:** Severe; most neonates die of respiratory/renal failure [PMID: 40704758; P 18780370].
- **Progression:** Largely congenital/static for malformations; Wilms tumor risk is progressive through early childhood.

- **Quality of life:** Severe impact — high neonatal mortality, and universal developmental delay plus cancer surveillance burden in survivors [PMID: 18780370].

## 4. Genetic / Molecular Information

- **Causal gene:** *DIS3L2* (2q37.1; HGNC:28648; UniProt Q8IYB7). Encodes a cytoplasmic 3′→5′ exoribonuclease (RNase II/RNB family, DIS3 homolog) lacking the PIN domain and exosome association [PMID: 22306653].
- **Variant classes:** nonsense (p.Arg43Ter), missense (p.Arg794His), frameshift (c.2109delC; c.1829_1830insC), and the recurrent **homozygous exon-9 deletion** via LINE-1 NAHR [PMID: 22306653; P 23486540 ; P 34964966 ; P 42040973 ].
- **Variant classification:** Reported variants classified **pathogenic** under ACMG/AMP criteria (e.g., PVS1+PS2+PM2) [PMID: 34964966].
- **Allele frequency:** Pathogenic alleles are exceedingly rare in population databases (gnomAD); no common founder allele established, though the exon-9 deletion recurs via a shared LINE-1 recombination mechanism.
- **Somatic vs germline:** Germline biallelic variants cause the syndrome; **somatic** *DIS3L2* mutations occur in both syndromic (second hit) and sporadic Wilms tumor [PMID: 22306653; P 35700413 ].
- **Functional consequence: Loss of function** (loss of exoribonuclease/RNA-surveillance activity). Tumor-suppressor behavior is demonstrated: overexpression suppresses and knockdown enhances cancer-cell growth [PMID: 22306653].
- **Modifier genes / epigenetics:** No specific modifier genes identified; residual enzyme activity modifies severity (inferred) [PMID: 42040973]. Unlike BWS, Perlman is **not** an imprinting disorder — 11p15/CDKN1C epigenetic alterations are excluded [PMID: 18780370].
- **Chromosomal abnormalities:** The locus is 2q37.1; the exon-9 deletion is a submicroscopic structural variant, not a visible cytogenetic abnormality [PMID: 23486540].

## 5. Environmental Information

**Not applicable.** No environmental factors, lifestyle factors, toxins, or infectious agents are implicated. Perlman syndrome is a fully genetic Mendelian disorder [PMID: 22306653; P 23613427].

## 6. Mechanism / Pathophysiology

**Ordered causal chain (initiating lesion → clinical manifestation):**

1. **Biallelic loss-of-function variants in *DIS3L2*** (homozygous/compound heterozygous) **result in** loss of functional cytoplasmic 3′→5′ oligo(U)-exoribonuclease [PMID: 22306653; P 25119025].
2. Loss of DIS3L2 catalytic activity **leads to** failure of Dis3l2-mediated decay (DMD) of 3′-oligouridylated RNAs [PMID: 27498873].
3. DMD failure **results in** accumulation of uridylated substrates: pre-let-7 and aberrant structured ncRNAs (7SL/SRP RNA, RMRP, rRNA, tRNA, snRNA, Y RNA) [PMID: 24141620; P 23594738; P 27647875; P 32457326].
   4a. Accumulation of aberrant 7SL RNA **leads to** impaired ER-targeted translation and ER calcium leakage, disturbing cell homeostasis and stem-cell differentiation [PMID: 32457326]. 4b. (Branch) Loss of DIS3L2 **leads to** increased **PI3K/AKT signaling** and growth-factor dysregulation (Idgf2/CHI3L1 homolog in *Drosophila*), **resulting in** cell overproliferation [PMID: 33370287]. 4c. (Branch) Loss of DIS3L2 **leads to** mitotic abnormalities, altered mitotic-checkpoint protein expression, and AKT–GSK3β dysregulation (*inferred to contribute* to overgrowth and neural-crest apoptosis) [PMID: 22306653; P 40500755].
4. Overproliferation and dysregulated growth signaling **result in** fetal overgrowth (macrosomia, visceromegaly, nephromegaly) and nephroblastomatosis [PMID: 18780370].
5. A **somatic second hit** at *DIS3L2* in a nephrogenic rest **leads to** Wilms tumor (two-hit model) [PMID: 35700413].

6. Note: mature **let-7 is unchanged** in DIS3L2-deficient cells/mice, so tumor suppression is **largely let-7-independent** — the operative driver is the broader RNA-surveillance failure converging on PI3K/AKT [PMID: 29950491].
7. **Molecular pathways:** PI3K/AKT (GO:0043491), AKT-GSK3β; LIN28–TUT4/7–DIS3L2 uridylation/decay axis.
8. **Cellular processes:** RNA catabolism/surveillance (GO:0006401), mitotic cell cycle regulation (GO:0007346), apoptosis (GO:0006915, neural crest), ER-targeted translation, calcium homeostasis.
9. **Protein dysfunction:** Loss of function of the exoribonuclease; open-funnel 3-RBD architecture recognizing oligoU over ~12 nt [PMID: 25119025].
10. **Subcellular compartments:** Cytoplasm (GO:0005737), endoplasmic reticulum (GO:0005783), spindle/mitotic apparatus.
11. **Cell types:** Renal progenitor/blastemal cells (nephroblastomatosis → Wilms), neural crest cells, pluripotent/stem cells.
12. **Suggested GO/CL terms:** GO:0000175 (3′-5′ exoribonuclease activity), GO:0071028 (nuclear mRNA surveillance — analogous cytoplasmic QC), GO:0043491 (PI3K/AKT); renal blastemal cell / nephron progenitor cell.

## 7. Anatomical Structures Affected

- **Primary organ: Kidney** (UBERON:0002113) — nephromegaly, renal dysplasia, nephroblastomatosis, Wilms tumor.
- **Secondary/other organs:** Liver and other viscera (visceromegaly; cholestasis reported) [PMID: 20726997]; lungs (respiratory failure as cause of death); brain/CNS (developmental delay, hypotonia); craniofacial structures (dysmorphism).
- **Body systems:** Renal/urinary, nervous, hepatobiliary, musculoskeletal (overgrowth), respiratory (secondary failure).
- **Tissue/cell level:** Renal metanephric blastema / nephrogenic rests (precursor to Wilms tumor); neural crest derivatives.
- **Subcellular:** Cytoplasm and ER (RNA decay, SRP-dependent translation, calcium homeostasis) [PMID: 32457326].
- **Localization/lateralization:** Nephromegaly and nephroblastomatosis are typically **bilateral**; Wilms tumor may be unilateral or bilateral.

- **Suggested UBERON terms:** UBERON:0002113 (kidney), UBERON:0002107 (liver), UBERON:0000955 (brain), UBERON:0002048 (lung).

## 8. Temporal Development

- **Onset: Congenital/prenatal** — detected in utero via polyhydramnios, macrosomia, ascites, and nephromegaly; often diagnosed prenatally or at birth [PMID: 24215131; P 38161545].
- **Progression:** Malformations are congenital; the dominant evolving risk is **Wilms tumor**, arising in infancy/early childhood from nephroblastomatosis.
- **Course/duration:** High neonatal mortality from respiratory/renal failure; survivors have a chronic, lifelong course marked by developmental delay and cancer surveillance [PMID: 40704758; P 18780370].
- **Critical period:** Early childhood is the window of maximal Wilms tumor risk and the rationale for intensive ultrasound surveillance [PMID: 39466169; P 34134020].

## 9. Inheritance and Population

- **Inheritance: Autosomal recessive** [PMID: 22306653].
- **Penetrance:** High/essentially complete for the overgrowth phenotype; Wilms tumor penetrance ~64% among neonatal survivors [PMID: 18780370].
- **Expressivity:** Variable, correlating with residual enzyme activity (genotype–phenotype gradient) [PMID: 42040973].
- **Epidemiology: Extremely rare** (fewer than ~40 reported patients); no reliable prevalence/incidence estimates — Orphanet lists it as <1/1,000,000. Both sexes affected; no strong sex bias documented.
- **Consanguinity:** Contributory but not required (2/7 reported sibships) [PMID: 18780370].
- **Founder effect / carrier frequency:** No established founder allele; carrier frequency unknown (too rare for reliable gnomAD estimates). The exon-9 deletion recurs via LINE-1-mediated NAHR rather than common ancestry [PMID: 23486540].

## 10. Diagnostics

- **Prenatal/imaging:** Ultrasound showing polyhydramnios, macrosomia, fetal ascites, bilateral nephromegaly, and characteristic renal appearance; CT/MRI of renal abnormalities [PMID: 18780370; P 20726997; P 24215131].
- **Laboratory:** No specific biomarker; cholestasis (elevated conjugated bilirubin) reported [PMID: 20726997].
- **Genetic testing (confirmatory):** Demonstration of **biallelic pathogenic *DIS3L2* variants**. Recommended approaches: whole-exome sequencing (WES) or targeted overgrowth/Wilms-predisposition gene panels; Sanger confirmation. **Copy-number/deletion analysis (e.g., MLPA, exon-level CMA) is essential** because large deletions (exon 9) are missed by sequence-only approaches [PMID: 22306653; P 23486540; P 34964966].
- **Histopathology:** Renal dysplasia, nephroblastomatosis/nephrogenic rests, and Wilms tumor on biopsy/nephrectomy specimens [PMID: 42535789].
- **Clinical criteria & differential diagnosis:** No formal consensus criteria; diagnosis is clinical-plus-molecular. Key differentials: **Beckwith-Wiedemann syndrome** (11p15 imprinting/CDKN1C), **Simpson-Golabi-Behmel syndrome** (GPC3), prune belly syndrome, and WT1-related syndromes (Denys-Drash) — distinguished by their molecular tests and by excluding 11p15/GPC3 alterations [PMID: 18780370; P 24215131; P 38161545; P 34106634].
- **Screening/surveillance:** Serial **renal/abdominal ultrasound ~every 3 months** in survivors for early Wilms tumor detection [PMID: 39466169; P 34134020].

## 11. Outcome / Prognosis

- **Mortality: High neonatal mortality** from respiratory and/or renal failure; the majority die in infancy [PMID: 40704758; P 18780370].
- **Survivor outcomes:** Among neonatal survivors, **~64% develop Wilms tumor and essentially all have developmental delay** [PMID: 18780370].
- **Prognostic factors:** Genotype is the dominant prognostic factor — **residual exoribonuclease activity** (partial-function/missense alleles) predicts prolonged survival, whereas the homozygous exon-9 deletion predicts poor survival [PMID: 42040973; P 40704758].
- **Complications:** Renal failure, respiratory failure, Wilms tumor, developmental/intellectual disability, cholestasis [PMID: 18780370; P 20726997].
- **Wilms-tumor-specific prognosis:** Wilms tumor in general has favorable survival with standard therapy; presence of nephrogenic rests did not worsen relapse/overall survival in unilateral WT cohorts [PMID: 42535789].

## 12. Treatment

There is **no disease-specific or curative therapy**; management is supportive and oncologic.

- **Supportive/neonatal care:** Respiratory and renal support for critically ill neonates; nutritional support; management of cholestasis [PMID: 40704758; P 20726997].
  (NCIT: supportive care C15277.)
- **Wilms tumor therapy:** Standard pediatric nephroblastoma protocols — **surgery (nephrectomy/nephron-sparing)**, **chemotherapy** (vincristine, actinomycin-D ± doxorubicin per SIOP/COG), and radiotherapy for higher-stage disease [PMID: 42535789; P 34503817].
  (NCIT: nephrectomy C15387; chemotherapy C15632.)

- **Surveillance as management:** Intensive renal ultrasound to enable early, organ-sparing tumor resection [PMID: 39466169; P 34134020].
- **Pharmacogenomics / advanced/targeted/gene/cell/RNA therapies: None established.** Mechanistically, the PI3K/AKT axis is a plausible future target (inferred from [PMID: 33370287]), but no clinical interventions exist.
- **Rehabilitation:** Developmental support/early intervention for survivors with developmental delay [PMID: 18780370].

## 13. Prevention

- **Primary prevention:** Not possible (germline genetic disorder). **Genetic counseling** for at-risk families, with 25% recurrence risk per pregnancy for carrier couples.
- **Reproductive options:** Prenatal diagnosis and **preimplantation genetic testing** where the familial variants are known; prenatal ultrasound can raise suspicion (polyhydramnios, macrosomia, nephromegaly, ascites) [PMID: 24215131; P 38161545].
- **Secondary/tertiary prevention: Renal ultrasound surveillance** (~every 3 months) in affected survivors to detect Wilms tumor early and prevent advanced-stage complications [PMID: 39466169; P 34134020].
- **Counseling:** Genetic counseling regarding autosomal recessive inheritance, carrier testing of parents/relatives, and the role of consanguinity (contributory but not required) [PMID: 18780370].

## 14. Other Species / Natural Disease

- **Orthologous genes:** *DIS3L2* is conserved; functional orthologs studied in mouse (*Dis3l2*), zebrafish (*dis3l2*), and *Drosophila* (*dis3L2*), and the ancestral *dis3* in *S. pombe* [PMID: 22306653; P 33370287; P 40500755].

- **Natural disease in other species:** No naturally occurring Perlman-syndrome-equivalent disease is documented in companion animals or wildlife (not reported in OMIA).
- **Comparative biology:** The DIS3L2 RNA-surveillance and PI3K/AKT overgrowth mechanism is **evolutionarily conserved from flies to humans**, validating cross-species modeling [PMID: 33370287].
- **Zoonotic/transmission:** Not applicable (non-infectious genetic disorder).

## 15. Model Organisms

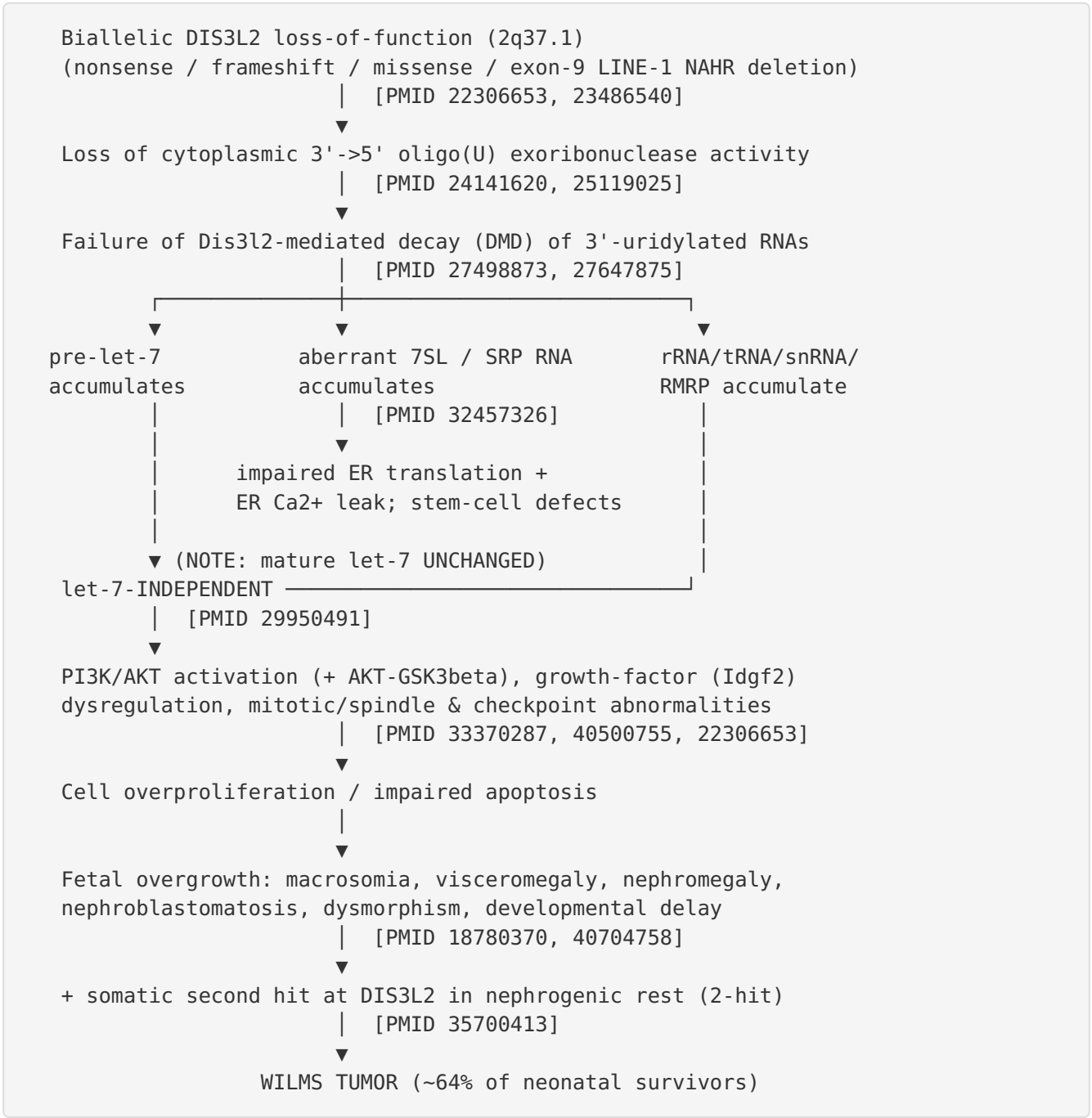
| Model | Type | Key findings | Recapitulation | PMID |
|---|---|---|---|---|
| *Drosophila* dis3L2-null / nuclease-dead | Invertebrate, genetic | Catalytic-activity-dependent overproliferation via Idgf2; PI3K/AKT link | Overgrowth/ proliferation mechanism | [PMID: 33370287] |
| Zebrafish dis3l2 morphant | Vertebrate | Neural crest apoptosis, mitotic/ spindle defects, Akt-GSK3β dysregulation | Developmental + signaling aspects | [PMID: 40500755] |
| Mouse embryonic stem cells / Dis3l2 knockdown | Mammalian cellular | pre-let-7 stabilization; mature let-7 unchanged; DMD of ncRNAs | Molecular/RNA-surveillance | [PMID: 23594738; P 29950491 P 27498873 ] |
| Human HEK-293T (kidney) DIS3L2 loss | In vitro human | Increased proliferation + PI3K/ AKT activation | Proliferation mechanism in kidney cells | [PMID: 33370287] |
| Human cell lines (CLIP uridylome; 7SL/ER) | In vitro human | Broad uridylome; 7SL/ SRP, ER translation, $Ca^{2+}$ leak | Subcellular mechanism | [PMID: 27647875; P 32457326 ] |

- **Model types available:** Invertebrate (fly), vertebrate (zebrafish), mammalian cellular (mouse ESC), and human cell lines.

- **Limitations:** No reported mouse model fully recapitulates the complete human syndromic phenotype (overgrowth + nephroblastomatosis + Wilms tumor) in a single system; models emphasize isolated mechanistic aspects. Loss of *DIS3L2* does **not** alter mature let-7, so let-7-centric models do not capture the tumor-suppressive mechanism [PMID: 29950491].
- **Resources:** MGI (mouse), ZFIN (zebrafish), FlyBase (*Drosophila*).

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## Mechanistic Model / Interpretation




The central interpretive insight is that Perlman syndrome is a **cytoplasmic RNA quality-control disease**. The historical emphasis on let-7 (because DIS3L2 is the pathway's terminal nuclease) is mechanistically incomplete: steady-state mature let-7 is unchanged on DIS3L2 loss [PMID: 29950491], so the tumor-suppressive and overgrowth phenotypes derive from the **broader surveillance failure** — accumulation of aberrant structured ncRNAs and consequent

PI3K/AKT-driven overproliferation. This reframes DIS3L2 as a general guardian of the cytoplasmic transcriptome whose loss produces growth dysregulation and cancer predisposition.

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# Evidence Base

| PMID | Role in this report | Evidence type |
|---|---|---|
| PMID: 22306653 | Gene discovery; DIS3L2 tumor suppressor; sporadic WT mutations | Human genetics + in vitro |
| PMID: 23613427 | Locus, inheritance, enzyme identity | Review |
| PMID: 23486540 | Exon-9 deletion via LINE-1 NAHR; diagnostic pitfall | Case/molecular |
| PMID: 24141620 | DIS3L2 = terminal nuclease of LIN28-TUT4/7 pathway | In vitro/mechanistic |
| PMID: 25119025 | Crystal structure; oligoU recognition | Structural |
| PMID: 23594738 | Dis3l2 degrades uridylated pre-let-7 (mESC) | Model organism |
| PMID: 27498873 | DMD as ncRNA quality-control pathway | Mechanistic |
| PMID: 27647875 | DIS3L2-dependent uridylome of structured ncRNAs | Human in vitro |
| PMID: 32457326 | 7SL/SRP, ER translation, $Ca^{2+}$ homeostasis | In vitro/mechanistic |
| PMID: 29950491 | Mature let-7 unchanged → let-7-independent | In vitro/model |
| PMID: 33370287 | PI3K/AKT-driven proliferation; conserved fly↔human | Model organism + human cells |
| PMID: 40500755 | Akt-GSK3β, neural crest apoptosis | Model organism (zebrafish) |
| PMID: 18780370 | Prognosis: 64% WT, developmental delay; BWS/SGBS exclusion | Human review/case series |
| PMID: 40704758 | High neonatal mortality; attenuated sibling cases | Human case report |
|  | Genotype-survival correlation; prolonged survival | Human case report |

| PMID | Role in this report | Evidence type |
|---|---|---|
| PMID: 42040973 | | |
| PMID: 35700413 | Two-hit Wilms tumor causation | Human case report |
| PMID: 34964966 | Compound het variants; ACMG classification | Human case/molecular |
| PMID: 39466169 | AACR WT surveillance guidelines | Guideline |
| PMID: 39320341 | AACR WT/hepatoblastoma surveillance update | Guideline |
| PMID: 34134020 | SIOP-Europe WT surveillance guidelines | Guideline |
| PMID: 42535789 | Nephrogenic rests and relapse risk | Human cohort |
| PMID: 24215131 | BWS/Perlman clinical overlap | Human case |
| PMID: 38161545 | DIS3L2 deletion; prenatal diagnosis; differentials | Human case |
| PMID: 20726997 | Cholestasis as novel feature | Human case |
| PMID: 34503817 | Pediatric cancer predisposition syndrome management | Review |

## Limitations and Knowledge Gaps

1. **Extreme rarity:** Fewer than ~40 molecularly/clinically characterized patients exist worldwide; prevalence, incidence, carrier frequency, and sex ratio are not reliably quantified. All clinical data come from small case series and reports, not EHR or registry cohorts.

2. **Prognosis estimates are small-sample:** The frequently cited "64% Wilms tumor" figure derives from a single review of neonatal survivors (small denominator) and may be subject to ascertainment bias [PMID: 18780370].
3. **Genotype–phenotype correlation is inferential:** The link between residual exoribonuclease activity and survival rests on a handful of case reports, not a systematic functional-genomic series [PMID: 42040973].
4. **Mechanistic gaps:** Although PI3K/AKT activation and let-7-independence are established, the exact molecular bridge from accumulated structured ncRNAs to PI3K/AKT activation is not fully resolved, and no model fully recapitulates the complete human syndrome.
5. **No disease-specific therapy or clinical trials:** Management is entirely supportive/oncologic; no targeted, gene, cell, or RNA therapies exist or are in trials.
6. **Epigenetics/omics:** No disease-specific methylation signature, proteomic, or metabolomic profile has been reported for patient tissue.

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## Proposed Follow-up Experiments / Actions

1. **Functional allele series:** Systematically express patient *DIS3L2* variants (nonsense, frameshift, missense, exon-9 deletion) and quantify residual exoribonuclease activity to formalize the genotype–severity correlation [extends

   P 42040973

   ].
2. **Conditional kidney mouse model:** Generate a renal-progenitor-specific *Dis3l2* knockout to test whether it recapitulates nephroblastomatosis/Wilms tumor and to map the two-hit timeline [extends

   P 22306653

   ;

   P 35700413

   ].
3. **Bridge the ncRNA→PI3K/AKT gap:** Use CLIP + phosphoproteomics in DIS3L2-null kidney cells to identify which accumulated uridylated substrate(s) drive PI3K/AKT activation [extends

   P 27647875

   ;

   P 33370287

   ].

4. **Therapeutic proof-of-concept:** Test PI3K/AKT pathway inhibitors in DIS3L2-deficient models for anti-proliferative effect, as a rationale for future precision intervention [extends P 33370287].
5. **Registry and surveillance audit:** Establish an international Perlman syndrome registry to refine prevalence, survival, and the yield/interval of renal ultrasound surveillance [extends P 39466169; P 34134020].
6. **Diagnostic standardization:** Formalize a testing algorithm mandating copy-number analysis (MLPA/exon-CMA) alongside WES to avoid missing exon-9 deletions [extends P 23486540].

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*Report compiled from 9 confirmed findings and 33 reviewed papers across 5 investigation iterations. Evidence types span human clinical/genetic, model organism (Drosophila, zebrafish, mouse), in vitro, and structural studies.*

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