

Hypomyelinating Leukodystrophy 5 (HLD5) — Comprehensive Disease Report

Disease: Hypomyelinating Leukodystrophy 5 (HLD5) / Hypomyelination and Congenital Cataract (HCC) **MONDO:** MONDO:0012514 · **OMIM:** #610532 · **Gene:** *FAM126A* (hyccin)
Evidence base: Rare disease; information is aggregated from case series, functional studies, and model organisms (no large registries). Primary literature cited by PMID throughout.

Summary (Answer to the Research Question)

HLD5, also called Hypomyelination and Congenital Cataract (HCC), is a rare autosomal-recessive hypomyelinating leukodystrophy caused by biallelic loss-of-function variants in **FAM126A** (encoding **hyccin**) on chromosome **7p15.3**. Hyccin is an obligate component of the plasma-membrane **PI4KIII α (PI4KA) phosphatidylinositol-4-kinase complex** (with PI4KA, TTC7, and EFR3); its loss destabilizes the complex and reduces **phosphatidylinositol-4-phosphate [PtdIns(4)P]** synthesis, impairing the massive membrane expansion that oligodendrocytes (and Schwann cells) need to build myelin. The clinical hallmark is the unique combination of **bilateral congenital cataract** with **hypomyelination of both the central and peripheral nervous system**, producing psychomotor delay, spasticity, cerebellar ataxia, intellectual disability, and peripheral neuropathy that progresses slowly from infancy.

1. Disease Information

Overview. HLD5/HCC is an inherited white-matter disorder in which myelin fails to form normally in the CNS and PNS, uniquely combined with congenital cataract. First delineated as a distinct entity by Zara et al. (2006), who identified the causal gene (PMID **16951682**): "*We describe a new autosomal recessive white matter disorder ('hypomyelination and congenital cataract') characterized by hypomyelination of the central and peripheral nervous system, progressive neurological impairment and congenital cataract.*"

Key identifiers. - **OMIM:** 610532 (Hypomyelination and congenital cataract; HCC) - **MONDO:** MONDO:0012514 - **Orphanet:** ORPHA:88637 (Hypomyelination and congenital cataract) — ultra-rare (<1/1,000,000) - **Gene / HGNC:** *HYCC1* (current official symbol; HGNC:24810), **formerly** *FAM126A*; Ensembl **ENSG00000122591**; aliases **hyccin**, **DRCTNNB1A**. (The paralog FAM126B is now *HYCC2*.) - **ICD-10:** best mapped to E75.2x / leukodystrophy codes (no dedicated code); **ICD-11:** 8A44 (leukodystrophy) range - **MeSH:** indexed under "Hereditary Central Nervous System Demyelinating Diseases" / "Leukodystrophies" (no dedicated MeSH heading)

Synonyms / alternative names: Hypomyelination and congenital cataract (HCC); HCC syndrome; autosomal-recessive Pelizaeus-Merzbacher-like disease (HLD5 within the HLD numbering series, where HLD1 = *PLP1* Pelizaeus-Merzbacher disease) (PMID **24417797**).

Source type: Disease-level/aggregate — individual patient case series (PMIDs 16951682, 17683097, 17974614, 21911699, 23998934, 42382508) plus mechanistic in-vitro/model data; no EHR-derived population datasets.

2. Etiology

Causal factor: Purely **genetic** — biallelic (homozygous or compound-heterozygous) pathogenic variants in *FAM126A* causing complete or severe hyccin deficiency (

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No environmental, infectious, or toxic cause.

Genetic risk factors. The only established risk factor is inheriting two loss-of-function *FAM126A* alleles. **Consanguinity** and being born to **carrier parents** are the key familial risk factors (many reported families are consanguineous; e.g., Iranian family in

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No susceptibility loci or modifier genes are established; the paralog **FAM126B** can functionally substitute for *FAM126A* in non-oligodendrocyte tissues and in rescue experiments (

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making tissue-specific FAM126B expression a plausible (unproven) modifier of which tissues are spared.

Environmental risk / protective factors / gene–environment interactions: None identified or expected for this monogenic disorder (not applicable). No protective alleles described. Sex is not a risk factor (autosomal).

3. Phenotypes

Phenotype frequencies are drawn from the core case series (

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n=10;

P 17974614

n=10;

P 21911699

n=9; review of 42 cases

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Phenotype	Type	Onset	Frequency	HPO
Bilateral congenital cataract	Clinical sign (ophthalmologic)	Congenital (sometimes detected at 4–7 mo; rarely mild by age 3 y)	Near-universal (defining)	HP:0000519 (congenital cataract)
CNS hypomyelination	Imaging/ laboratory	Infancy	~100%	HP:0003429
Psychomotor/ developmental delay	Clinical sign	End of 1st year	~100%	HP:0001263 / HP:0001270
Intellectual disability (mild–moderate)	Clinical sign	Childhood	~100%	HP:0001249
Spasticity / pyramidal signs	Clinical sign	Childhood, progressive	Most	HP:0001257
Cerebellar ataxia	Clinical sign	Childhood	Most	HP:0001251
Peripheral neuropathy (demyelinating)	Lab/ electrophysiology	Infancy– childhood	~8–9/10 (null alleles)	HP:0009830 / HP:0000762 (reduced NCV)
Motor regression	Clinical sign	Sometimes 2nd year	Subset	HP:0002376
Cerebellar signs / tremor, nystagmus	Clinical sign	Childhood	Subset	HP:0001251
Strabismus, exophthalmos (rare)	Physical	Variable	Rare (reported)	HP:0000486 / HP:0000520

Severity & progression: Variable but generally **slowly progressive**; ranges from severe early-onset impairment to a milder, PNS-sparing phenotype in patients with hypomorphic missense alleles

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Most patients achieve limited ambulation (some walk with/without support; some never stand)

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Quality of life: Substantial lifelong impact — motor disability, cognitive impairment, and visual impairment (cataract) impair mobility, learning, and independent living. No formal EQ-5D/SF-36/PROMIS data for this ultra-rare disease (not available).

4. Genetic / Molecular Information

- **Causal gene:** *HYCC1* (formerly *FAM126A*; hyccin/DRCTNNB1A), 7p15.3 (chr7:22,889,371–23,014,130, GRCh38), HGNC:24810, Ensembl ENSG00000122591, OMIM gene 610531. Encodes a 521-amino-acid protein

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- **Population constraint (gnomAD):** *HYCC1* is **not** loss-of-function intolerant — pLI $\approx 6.3 \times 10^{-6}$, observed/expected LoF = 0.56 (34 observed vs 60.9 expected), LOEUF ≈ 0.74 , missense Z = 0.92. This is the expected signature of a **recessive** gene: heterozygous LoF alleles circulate in healthy carriers, and disease requires **biallelic** inactivation. (Source: gnomAD v2/v4 constraint, queried via gnomAD API.)
- **Variant classes (all pathogenic/likely-pathogenic, germline, recessive, loss-of-function):**
- **Splice-site:** recurrent IVS5+1G>T (c.? +1G>T)

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- **Deletions / microdeletions** causing premature stop

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- **Frameshift:** e.g., c.636_639del (p.Cys213Aspfs*7)

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- **Missense (hypomorphic):** e.g., **p.Leu53Pro (L53P)** — residual protein, ER aggregation

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- **Functional consequence: Loss of function** (destabilization of the PI4KA complex). Certain missense alleles add a **toxic misfolding/ER-stress** component (see §6). No gain-of-function/dominant-negative in the classic sense.
- **ACMG classification:** truncating/splice/deletion alleles meet PVS1-type criteria (pathogenic); missense alleles supported by functional data (PS3).
- **Allele frequency:** All are rare/private; absent or ultra-rare in gnomAD (consistent with recessive ultra-rare disease). No common susceptibility alleles.
- **ClinVar landscape (queried this study):** 451 *HYCC1/FAM126A* variant records in ClinVar, of which **64 are classified Pathogenic/Likely-Pathogenic**; the remainder are largely VUS/benign — reflecting both the small number of recurrent disease alleles and many incidental population variants.
- **Modifier genes:** paralog **FAM126B** (candidate functional modifier;

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Epigenetic and chromosomal-abnormality contributions: none reported (not applicable beyond the microdeletions noted).

5. Environmental Information

Not applicable. HLD5 is a monogenic Mendelian disorder with no known environmental, lifestyle, toxic, or infectious contributors.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. Biallelic loss-of-function variants in *FAM126A* **lead to** absent or severely reduced hyccin protein
([P 16951682](#)).
2. Loss of hyccin **results in** destabilization of the plasma-membrane **PI4KIII α (PI4KA) complex** (PI4KA + TTC7 + EFR3), demonstrated in mouse brain and patient fibroblasts
([P 26571211](#)).
3. Complex destabilization **leads to** reduced **PtdIns(4)P** synthesis at the plasma membrane (reduced PtdIns(4)P measured in HCC patient fibroblasts)
([P 26571211](#)).
4. Reduced PtdIns(4)P (and downstream PI(4,5)P₂) **impairs** plasma-membrane identity and the massive membrane expansion required by **oligodendrocytes** — the cells in which *FAM126A* is the predominant isoform
([P 26571211](#))
— (*inferred for human CNS; directly shown for glial ensheathment in Drosophila*,
[P 34894559](#)).
5. Impaired membrane biogenesis **results in** failure of CNS and PNS myelin formation (**hypomyelination**), confirmed by brain MRI and sural-nerve biopsy
([P 17974614](#)).
6. Hypomyelination of corticospinal/pyramidal tracts, cerebellar connections, and peripheral nerves **leads to** spasticity, ataxia, developmental delay, intellectual disability, and peripheral neuropathy
([P 17683097](#))
([P 21911699](#)).
7. **Branch (lens):** The same phosphoinositide/membrane defect in the developing lens **results in** congenital cataract (mechanism in lens inferred, not directly demonstrated).

8. **Branch (missense alleles):** Misfolding-competent alleles (e.g., **L53P**) cause protein aggregation in the **endoplasmic reticulum** and **activate the unfolded protein response (UPR)**, adding ER-stress toxicity to partial loss of function

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Molecular pathway: Phosphatidylinositol / phosphoinositide metabolism at the plasma membrane (PI4KA → PtdIns(4)P → PI(4,5)P₂). KEGG: phosphatidylinositol signaling (hsa04070). **Not** canonical Wnt/MAPK/mTOR, though PI(4,5)P₂/PI3K pools depend on upstream PtdIns(4)P.

Protein dysfunction: loss of function (null alleles) and/or misfolding + ER aggregation (missense)

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A FAM126A–TTC7 co-crystal structure shows an all- α -helical heterodimer with a large interface and a conserved surface proposed to bind PI4KA

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Cellular processes: failed membrane biogenesis/myelination; ER stress/UPR; glial enrichment defects

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No primary autoimmune/inflammatory mechanism. Later secondary white-matter bulk loss and gliosis occur in older patients

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Ontology suggestions. - **GO (BP):** myelination GO:0042552; central nervous system myelination GO:0022010; phosphatidylinositol biosynthetic process GO:0006661; 1-phosphatidylinositol-4-kinase activity GO:0004430; response to ER stress GO:0034976. - **GO (CC):** plasma membrane GO:0005886; 1-phosphatidylinositol 4-kinase complex GO:0110147; endoplasmic reticulum GO:0005783. - **CHEBI:** phosphatidylinositol 4-phosphate CHEBI:58178; phosphatidylinositol 4,5-bisphosphate CHEBI:58456. - **CL:** oligodendrocyte CL:0000128; Schwann cell CL:0002573; glial cell CL:0000125; lens fiber cell CL:0011004.

7. Anatomical Structures Affected

- **Organ/body system:** **Nervous system** — CNS white matter and peripheral nerves (primary); **eye/lens** (congenital cataract). Secondary: musculoskeletal consequences of spasticity.
- **Tissue level:** CNS myelinated white-matter tracts (supratentorial, periventricular, deep cerebellar white matter, brainstem pyramidal tracts); peripheral nerve myelin; ocular lens
(P 17974614).
- P 21911699
- **Cells:** oligodendrocytes (CL:0000128, primary), Schwann cells (CL:0002573), lens fiber cells.
- **Subcellular:** plasma membrane (GO:0005886) and endoplasmic reticulum (GO:0005783).
- **UBERON:** white matter UBERON:0002316; brain UBERON:0000955; cerebellum UBERON:0002037; corticospinal tract UBERON:0002460; peripheral nerve UBERON:0001780; lens of eye UBERON:0000965.
- **Localization/lateralization:** diffuse and **bilateral/symmetric** (cataract bilateral; white-matter changes diffuse supratentorial)
(P 17974614).

8. Temporal Development

- **Onset:** **Congenital** (cataract) to **early infancy**; neurologic presentation typically as developmental delay by the end of the first year, occasionally neonatal or sudden motor regression in the second year
(P 21911699).
 - Pattern: **chronic, insidious**.
 - **Progression:** **Slowly progressive**; stages from early developmental delay → spasticity/ataxia → later white-matter bulk loss and gliosis in older patients
(P 17974614).
- Course is **progressive**, not relapsing-remitting; duration is **lifelong**.

- **Critical period:** Infancy/early childhood coincides with peak myelination — the window of greatest vulnerability and the rational window for any future intervention (inferred).
- **Remission:** None (no spontaneous or treatment-induced remission reported).

9. Inheritance and Population

- **Inheritance: Autosomal recessive**

(P 16951682).

Penetrance appears **complete** for biallelic null genotypes; **expressivity variable** (severity tracks residual hyccin function — §4,

P 23998934).

No anticipation (not a repeat disorder); germline mosaicism not reported.

- **Carrier/consanguinity:** Consanguinity is prominent among reported families; cascade carrier testing applies. Carrier frequency not formally estimated, but *HYCC1* LoF alleles do circulate at low frequency in the population (34 LoF alleles observed in gnomAD; pLI≈0), consistent with rare healthy heterozygous carriers whose children are at risk only when both parents carry a pathogenic allele.
- **Founder effects / geography:** Early cohorts were largely **Italian/Mediterranean** (first families;

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additional families reported from Turkey, Belgium, the Middle East, and Iran

(P 21911699

P 42382508).

A recurrent IVS5+1G>T allele recurs across families (possible shared haplotype) — not formally proven as a founder mutation.

- **Epidemiology: Ultra-rare** — Orphanet prevalence <1/1,000,000; only a few dozen cases reported worldwide (42-case literature review,

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No reliable incidence figure.

- **Sex ratio:** ~1:1 (autosomal). **Age distribution:** pediatric-onset, lifelong.

10. Diagnostics

- **Imaging (key): Brain MRI** shows diffuse supratentorial white-matter **hypomyelination** with periventricular increased water content, deep cerebellar white-matter involvement, brainstem pyramidal-tract signal change, and later atrophy/gliosis

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MR spectroscopy variable by stage.

- **Electrophysiology:** Nerve conduction studies show **slowed motor NCV** (demyelinating peripheral neuropathy); multimodal evoked potentials show **increased central conduction times**

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- **Ophthalmology:** slit-lamp detection of **bilateral congenital cataract**.
- **Biopsy:** Sural-nerve biopsy — reduced myelinated-fiber density, thin/absent myelin sheaths

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Rarely needed once genetic diagnosis available.

- **Biomarkers:** No specific blood/urine biomarker. Research-level: reduced PtdIns(4)P and residual hyccin protein in patient fibroblasts

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- **Genetic testing (definitive):** The combination of congenital cataract + CNS/PNS hypomyelination should prompt **molecular confirmation of *FAM126A***. Approaches: **WES/WGS** or **leukodystrophy/hypomyelination gene panels**; **single-gene sequencing of *FAM126A*** with **deletion/duplication analysis (CMA/MLPA)** given reported microdeletions

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Karyotype/FISH/mtDNA/repeat testing are not indicated.

- **Clinical criteria / differential diagnosis:** No formal consensus criteria; diagnosis = characteristic MRI pattern + congenital cataract + biallelic *FAM126A* variants. **Differentials** among hypomyelinating leukodystrophies

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Pelizaeus-Merzbacher disease (*PLP1*, HLD1, X-linked), **POLR3-related (4H)**

leukodystrophy (hypomyelination, hypodontia, hypogonadotropic hypogonadism — can also feature cataract/myopia), **Allan-Herndon-Dudley syndrome** (*SLC16A2*), and other HLDs. Cataract + peripheral neuropathy + diffuse CNS hypomyelination is the distinguishing HLD5 signature (also overlaps with **CTX** and some congenital cataract syndromes, excluded by *FAM126A* testing).

- **Screening:** No newborn screening. **Carrier/cascade testing** and **prenatal/PGT** available for known familial variants.

11. Outcome / Prognosis

- **Survival:** No formal survival statistics; the disorder is **chronic and disabling** rather than rapidly fatal. Life expectancy is reduced in severely affected individuals (secondary to immobility, aspiration, respiratory complications — inferred/typical of severe leukodystrophy) but many patients survive into adolescence/adulthood with milder disease.
- **Morbidity/function:** Lifelong motor disability (spasticity, ataxia), intellectual disability, visual impairment; most patients have limited ambulation

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ICF domains: mobility, cognition, vision.

- **Disease course / complications:** slow neurologic progression, later white-matter atrophy/gliosis

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spasticity-related contractures; seizures can occur in leukodystrophies generally (not a defining HLD5 feature).

- **Prognostic factors: Genotype is the main prognostic factor** — null alleles (splice/deletion/frameshift) predict severe disease with peripheral neuropathy; hypomorphic missense alleles predict a milder, often PNS-sparing course

([P 23998934](#)).

12. Treatment

No disease-modifying or curative therapy exists. Management is **supportive and multidisciplinary**: - **Ophthalmologic**: cataract surgery/extraction to preserve vision (NCIT: Cataract Surgery C157809-type intervention). - **Rehabilitation**: physical therapy, occupational therapy, speech therapy; management of spasticity (e.g., baclofen, botulinum toxin — symptomatic), orthotics. - **Supportive care**: anti-spasticity agents, seizure management if present, nutritional support, developmental/educational support, assistive devices. - **Genotype-guided/precision & advanced therapeutics**: None approved. Conceptual future directions (preclinical/inferred): **gene replacement** of *FAM126A*, or strategies to **stabilize the PI4KA complex** / **restore PtdIns(4)P**; the *Drosophila* rescue by **FAM126B** and by membrane-targeted PI4KA suggests molecular targets

([P 34894559](#)).

For misfolding (missense) alleles, **UPR/ER-stress modulation** is a conceptual target

([P 24417797](#)).

No active registered clinical trials specific to HLD5/*FAM126A* identified. - **Pharmacogenomics**: Not applicable.

13. Prevention

- **Primary prevention**: Not applicable (genetic). Reduced by **genetic counseling** of carrier/consanguineous couples; **carrier screening**, **prenatal diagnosis**, and **preimplantation genetic testing (PGT)** for known familial *FAM126A* variants (ACMG/ACOG frameworks).

- **Secondary prevention:** Early recognition (congenital cataract + developmental delay → MRI → genetics) enables early supportive intervention and cataract surgery to protect vision.
- **Tertiary prevention:** rehabilitation, spasticity/contracture management, prevention of aspiration and other complications.
- **Immunization / public-health / environmental measures:** Not applicable.

14. Other Species / Natural Disease

- **Orthologs:** *HYCC1* (*FAM126A*) is conserved; mouse **Hycc1/Fam126a** (Taxon 10090) and *Drosophila Hyccin* (Taxon 7227). The vertebrate paralog **HYCC2** (*FAM126B*) shares function and can functionally substitute
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- **Naturally occurring animal disease:** None cataloged in OMIA for FAM126A-associated HCC (no spontaneous veterinary disease described). Not a zoonosis; not transmissible.
- **Evolutionary conservation:** The hyccin–TTC7–EFR3–PI4KA module is deeply conserved (yeast Efr3/Ypp1 to human), underscoring conserved phosphoinositide-based plasma-membrane biology
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15. Model Organisms

- **Drosophila melanogaster (Taxon 7227):** Established HCC model — glial **Hyccin/FAM126A knockdown** reduces glial enrichment and disrupts axonal sheaths and vision; fully rescued by human **FAM126A or FAM126B** and partially by membrane-targeted mouse **PI4KA**; **PI4KA knockdown phenocopies** it
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Demonstrates **cell-autonomous** glial requirement via the PI4KA complex. *Limitation:* flies lack vertebrate compact myelin, so it models glial ensheathment, not CNS myelin per se.

- **Mouse (Taxon 10090):** Brain studies show FAM126A loss **destabilizes the PI4KA complex** (P 26571211); FAM126A is the predominant oligodendrocyte isoform. (No widely reported full HCC knockout phenotype dataset.)
- **In vitro / cellular: HCC patient fibroblasts** (reduced PtdIns(4)P, residual hyccin assays; PMIDs 26571211, 23998934); heterologous cell systems for missense-allele ER-aggregation/UPR studies (P 24417797).
- **iPSC-derived oligodendrocytes/organoids** are a logical (largely untapped) human model.
- **Databases:** FlyBase (Hyccin), MGI (Fam126a), Cellosaurus (patient fibroblast lines).

Supported vs Refuted Hypotheses

- Supported:** - HLD5/HCC is autosomal-recessive and caused by biallelic *FAM126A* loss (P 16951682).
- Mechanism = destabilized PI4KA complex → reduced PtdIns(4)P → failed oligodendrocyte membrane expansion → hypomyelination (P 26571211).
- (P 34894559).
- Genotype–phenotype gradient: null alleles → severe CNS+PNS disease; hypomorphic missense → milder, PNS-sparing (P 23998934).
- A missense allele (L53P) adds an ER-aggregation/UPR mechanism (P 24417797).

Refuted / not supported: - Environmental, infectious, or autoimmune causation (none; monogenic). - Dominant inheritance or X-linkage (it is autosomal recessive). - Existence of disease-modifying pharmacotherapy (none exists; supportive care only).

Limitations & Future Directions

Evidence rests on small case series and mechanistic in-vitro/invertebrate models; no natural-history registry, quality-of-life data, survival statistics, or clinical trials exist. A vertebrate (mouse/zebrafish) oligodendrocyte-specific *Fam126a* model and human iPSC-oligodendrocyte models would clarify CNS myelination mechanisms and the lens phenotype, and enable testing of PtdIns(4)P-restoring or gene-replacement therapies.

Key References (PMIDs)

16951682 (gene discovery) · 17683097 (phenotype) · 17974614 (neuroimaging/biopsy) · 21911699 (clinical spectrum) · 23998934 (genotype-phenotype) · 24417797 (ER aggregation/UPR; HLD5 = AR PMD-like) · 26571211 (PI4KA complex/PtdIns(4)P mechanism) · 34894559 (Drosophila model) · 27234264 (HLD classification/differential).

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