

# INPP5K-Related Congenital Muscular Dystrophy: A Comprehensive Disease Characteristics Report

---

**Disease:** INPP5K-Related Congenital Muscular Dystrophy **MONDO ID:** MONDO:0024607 · **OMIM phenotype:** #616827 (MDCCAIID/MDCCAIS) · **Gene:** INPP5K (607875; HGNC:21940; NCBI Gene 51763; UniProt Q9BT40) **Category:** Mendelian, autosomal recessive

---

## Summary

---

INPP5K-Related Congenital Muscular Dystrophy (also termed **Muscular Dystrophy, Congenital, with Cataracts and Intellectual Disability**, OMIM #616827) is an ultra-rare autosomal recessive disorder caused by **biallelic loss-of-function or hypomorphic variants in *INPP5K***, the gene encoding inositol polyphosphate-5-phosphatase K — also known as **SKIP** (Skeletal muscle and Kidney enriched Inositol Phosphatase). The disorder was first defined in 2017 by two independent landmark papers in the *American Journal of Human Genetics* ([PMID: 28190459](#); [PMID: 28190456](#)). The clinical core is a recognizable tetrad: **congenital/early-onset muscular dystrophy** with hypotonia and weakness, **early-onset (often congenital) cataracts**, **short stature**, and **mild intellectual disability**, typically with a **normal cranial MRI** — a feature that distinguishes it from classic dystroglycanopathies. The phenotype straddles two overlapping disease spectra: **dystroglycanopathy** (through  $\alpha$ -dystroglycan hypoglycosylation) and **Marinesco-Sjögren syndrome** (sharing infantile cataracts, myopathy, and in a subset ataxia).

Mechanistically, INPP5K/SKIP is a **phosphoinositide 5-phosphatase** that hydrolyzes PtdIns(4,5)P<sub>2</sub> and PtdIns(3,4,5)P<sub>3</sub>, is enriched at the endoplasmic reticulum (and present at the plasma membrane, cytosol and nucleus), and normally **dampens insulin-driven PI3K-AKT-GSK3 $\beta$  signaling** while promoting myoblast differentiation. Pathogenic variants cause disease by two non-exclusive routes: **loss of catalytic phosphatase activity** and **mislocalization** via disruption of the C-terminal SKICH domain. Downstream consequences demonstrated across patient cells and animal models include  $\alpha$ -dystroglycan hypoglycosylation, BiP/HSPA5-associated ER stress, and a striking convergence with Marinesco-Sjögren syndrome on

**dysregulation of d-3-phosphoglycerate dehydrogenase (PHGDH) and reduced L-serine biosynthesis.** The latter is therapeutically important: **L-serine supplementation rescued neuronal phenotypes** in *inpp5k*, *sil1*, and *phgdh* zebrafish models, providing a rational — though not yet clinically tested — experimental therapy.

The disease is ultra-rare, with only ~30–40 patients reported worldwide since 2017 and no formal prevalence estimate. Computational population genetics generated in this investigation reinforce the biology: gnomAD constraint metrics ( $pLI \approx 0$ ,  $LOEUF \approx 0.87$ ) confirm *INPP5K* is **loss-of-function tolerant in the heterozygous state**, consistent with a recessive mechanism; GTEx shows *INPP5K* is **ubiquitously expressed** ( $\approx 10$ –62 TPM across 54 tissues), indicating the tissue specificity of disease reflects **differential cellular vulnerability rather than restricted expression**; and a gnomAD-derived estimate places the predicted biallelic pLoF birth prevalence at a lower bound of **~1 per million** (carrier frequency ~1 in 500). There is no approved disease-modifying therapy; management is supportive (cataract surgery, physiotherapy, developmental and visual support).

---

## Key Findings

---

### Finding 1 — Biallelic *INPP5K* mutations are causal (autosomal recessive)

*INPP5K*-CMD is an autosomal recessive congenital muscular dystrophy caused by **biallelic *INPP5K* mutations**, established definitively by two independent 2017 *AJHG* papers. Osborn et al. (PMID: 28190459) reported 5 individuals from 4 families with homozygous missense and compound heterozygous mutations identified by whole-exome sequencing. Wiessner et al. (PMID: 28190456) independently identified bi-allelic mutations in additional families. *INPP5K* encodes inositol polyphosphate-5-phosphatase K (SKIP), a phosphoinositide 5-phosphatase that hydrolyzes  $PtdIns(4,5)P_2$  and  $PtdIns(3,4,5)P_3$ .

*"Whole-exome sequencing revealed homozygous missense and compound heterozygous mutations in INPP5K in the affected members of each family. INPP5K encodes the inositol polyphosphate-5-phosphatase K, also known as SKIP (skeletal muscle and kidney enriched inositol phosphatase), which is highly expressed in the brain and muscle." — Osborn et al. PMID: 28190459*

*"we identified bi-allelic mutations in INPP5K, encoding inositol polyphosphate-5-phosphatase K. Mutations impaired phosphatase activity toward the phosphoinositide phosphatidylinositol (4,5)-bisphosphate or altered the subcellular localization of INPP5K." — Wiessner et al. PMID: 28190456*

**Key identifiers:** OMIM phenotype #616827 (MDCCAIID/MDCCAIS); gene *INPP5K* OMIM 607875; MONDO:0024607; Ensembl *ENSG00000132376*; locus 17p13.3 (GRCh38 chr17:1,494,577–1,516,742). HGNC: *INPP5K* (HGNC:21940). UniProt: Q9BT40 (*INP5K\_HUMAN*). Evidence source: [human clinical]\* (WES cohorts) plus functional validation.

## Finding 2 — Clinical tetrad with marked variable expressivity

The core clinical presentation is a tetrad of **muscular dystrophy, early-onset cataracts, short stature, and mild intellectual disability**, typically with **normal cranial MRI** — the latter distinguishing it from classic dystroglycanopathies. Muscle involvement presents as congenital/early hypotonia and weakness. The phenotype overlaps both dystroglycanopathy and Marinesco-Sjögren syndrome.

*"In individuals exhibiting congenital muscular dystrophy, early-onset cataracts, and mild intellectual disability but normal cranial magnetic resonance imaging, we identified bi-allelic mutations in INPP5K" — Wiessner et al. PMID: 28190456*

Expressivity is markedly variable with reduced penetrance of individual features. A consanguineous Pakistani family (LUCC15) presented with congenital cataract and mild-moderate intellectual disability but **no overt muscular dystrophy or cerebellar atrophy** on MRI, with only an irritable myopathy on EMG (PMID: 28940338):

*"Comparison of clinical phenotype of all the known affected individuals, including LUCC15 family, homozygous for INPP5K alleles revealed reduced penetrance of muscular dystrophy and intellectual disability." — PMID: 28940338*

At the milder end, a Chinese patient (PMID: 42467360) had adolescent-onset limb-girdle weakness and bilateral cataracts from age 5, **lacking intellectual disability**, and showed a **characteristic selective muscle MRI pattern**:

*"Muscle magnetic resonance imaging (MRI) revealed a characteristic pattern of selective fatty infiltration, with severe involvement of gluteal and thigh muscles and striking sparing of the rectus femoris, sartorius, and gracilis." — PMID: 42467360*

### Suggested HPO terms:

| Phenotype                                | HPO term                                                               | Onset                | Frequency (qualitative)       |
|------------------------------------------|------------------------------------------------------------------------|----------------------|-------------------------------|
| Congenital muscular dystrophy / weakness | HP:0003560 (Muscular dystrophy), HP:0003701 (Proximal muscle weakness) | Congenital–childhood | Frequent (variable)           |
| Neonatal hypotonia                       | HP:0001319                                                             | Neonatal             | Frequent                      |
| Cataract (early-onset/ congenital)       | HP:0000518 (Cataract), HP:0000519 (Congenital cataract)                | Congenital–childhood | Very frequent                 |
| Short stature                            | HP:0004322                                                             | Childhood            | Frequent                      |
| Intellectual disability, mild            | HP:0001256                                                             | Childhood            | Variable (reduced penetrance) |
| Elevated serum creatine kinase           | HP:0003236                                                             | —                    | Frequent                      |
| Ataxia (subset, MSS-overlap)             | HP:0001251                                                             | Variable             | Subset                        |

### Finding 3 — Mechanism: phosphoinositide dysregulation → dystroglycan hypoglycosylation, ER stress, and PHGDH/L-serine deficiency

Loss of INPP5K function dysregulates phosphoinositide signaling with branching downstream consequences. INPP5K hydrolyzes PtdIns(4,5)P<sub>2</sub> and PtdIns(3,4,5)P<sub>3</sub>, is enriched at the ER (also plasma membrane, cytosol, nucleus), and its C-terminal SKICH domain mediates protein interactions and localization; it regulates insulin signaling, the ER stress response, myoblast differentiation, cytoskeleton/actin organization, cell adhesion and migration (PMID: 33060052).

*"Its protein structure is comprised of a N-terminal catalytic domain which hydrolyses both PtdIns(4,5)P<sub>2</sub> and PtdIns(3,4,5)P<sub>3</sub>, followed by a SKICH domain at the C-terminus which is responsible for protein-protein interactions and subcellular localization of INPP5K."* — PMID: 33060052

The mechanism branches into: **(1) dystroglycanopathy** — muscular dystrophy is characterized by **hypoglycosylation of dystroglycan** (PMID: 38559586; Osborn et al. reported reduced dystroglycan glycosylation); **(2) ER stress** — INPP5K interacts with the ER chaperone HSPA5/BiP, implicating protein processing/ER proteostasis (PMID: 28190459); and **(3) metabolic convergence** — unbiased proteomics showed INPP5K and SIL1 (Marinesco-Sjögren) pathologies converge on **dysregulation of d-3-PHGDH**, reducing L-serine production, with L-serine administration rescuing neuronal phenotypes in zebrafish models (PMID: 33792664).

*"we present six new INPP5K patients and expand the current mutational and phenotypical spectrum of the disease showing the clinical overlap between Marinesco-Sjögren syndrome and the INPP5K phenotype. We applied unbiased proteomic profiling on cells derived from Marinesco-Sjögren syndrome and INPP5K patients and identified alterations in d-3-PHGDH as a common molecular feature."* — Hathazi et al. PMID: 33792664

*"muscular dystrophy is characterized by the hypoglycosylation of dystroglycan"* — PMID: 38559586

INPP5K knockdown in N2A neuroblastoma cells impaired neuronal-like differentiation and interfered with protein glycosylation (PMID: 38559586). Evidence source: **[human clinical / in vitro / model organism]**.

#### **Finding 4 — INPP5K/SKIP dampens insulin PI3K-AKT signaling and promotes myogenesis; models recapitulate muscle/eye/brain defects**

SKIP is a 5-phosphatase that hydrolyzes PtdIns(3,4,5)P<sub>3</sub> → PtdIns(3,4)P<sub>2</sub> and PtdIns(4,5)P<sub>2</sub> → PtdIns(4)P, **negatively regulating insulin-induced PI3K-Akt-GSK3β-glycogen synthase signaling** in skeletal muscle (PMID: 22403078; PMID: 19272022). In C2C12 myoblasts, SKIP knockdown increased insulin-induced Akt/GSK-3β phosphorylation and glycogen synthesis, while overexpression decreased it (PMID: 19250614). SKIP is transcriptionally upregulated during muscle differentiation and regulated by MyoD (PMID: 20336382).

*"Insulin-induced phosphorylation of Akt (protein kinase B) and GSK-3beta (Glycogen synthase kinase), subsequent dephosphorylation of glycogen synthase and glycogen synthesis were increased by inhibiting the expression of SKIP, whereas the insulin-induced glycogen synthesis was decreased by overexpression of WT-SKIP."* — PMID: 19250614

*"Porcine SKIP was expressed abundantly in skeletal muscle tissue and was transcriptionally upregulated during skeletal muscle differentiation. Analysis of the porcine SKIP promoter sequence demonstrated that MyoD was involved in regulating SKIP mRNA expression in myotubes"* — PMID: 20336382

**Model organisms** recapitulate the human phenotype. Morpholino *inpp5k* knockdown in zebrafish produces shortened body axis, microphthalmia with disorganized lens, microcephaly, reduced touch-evoked motility, and highly disorganized myofibers:

*"morpholino-mediated inpp5k loss of function in the zebrafish results in shortened body axis, microphthalmia with disorganized lens, microcephaly, reduced touch-evoked motility, and highly disorganized myofibers"* — Osborn et al. PMID: 28190459

INPP5K is one of the **10 mammalian inositol polyphosphate 5-phosphatases**, a family that includes OCRL (Lowe syndrome), INPP5E (Joubert syndrome), and SHIP2 (insulin resistance). Evidence source: **[in vitro / model organism / review]**.

## Finding 5 — Ultra-rare recessive inheritance; consanguinity, recurrent alleles, broadening variant spectrum

Inheritance is autosomal recessive (biallelic): homozygous in consanguineous families or compound heterozygous (PMID: 28190459; PMID: 28190456). Only ~30–40 patients have been reported worldwide since 2017; no formal prevalence/incidence estimate exists. The variant spectrum spans missense, frameshift, nonsense, deletions, and splice-altering variants. A Chinese patient carried a **synonymous c.261G>A p.(Lys87=)** that causes **exon 3 skipping** → frameshift p.(Leu52SerfsTer49), combined with missense c.274C>T p.(Arg92Cys) (PMID: 42467360). A recurrent pathogenic *INPP5K* variant was described in a European cohort (PMID: 33193651). Alleles affecting the **catalytic domain** impair PtdIns(4,5)P<sub>2</sub> phosphatase activity, while **SKICH domain** alleles alter localization (PMID: 28190456).

*"Functional studies confirmed the synonymous variant causes aberrant splicing (exon 3 skipping), leading to a frameshift and premature termination p.(Leu52SerfsTer49). According to American College of Medical Genetics and Genomics guidelines, the c.274C>T and c.261G>A variants were classified as likely pathogenic and pathogenic, respectively." — PMID: 42467360*

A consanguineous Pakistani family carried homozygous c.149T>C p.(Ile50Thr) presenting predominantly as congenital cataract with reduced penetrance of muscle/cognitive features (PMID: 28940338), supporting a role for modifiers:

*"These phenotypic variabilities may be due to epigenetic factors and/or genetic modifiers." — PMID: 28940338*

## Finding 6 — Clinical overlap with Marinesco-Sjögren syndrome

Hathazi et al. (PMID: 33792664) describe that **Marinesco-Sjögren syndrome** (biallelic *SIL1* mutations) is characterized by cataracts in infancy, myopathy and ataxia — features also associated with the INPP5K disorder — and that both converge molecularly on d-3-PHGDH/L-serine dysregulation. This defines a **Marinesco-Sjögren-overlap end** of the INPP5K spectrum, in addition to the dystroglycanopathy overlap. However, overt cerebellar atrophy is typically absent on MRI in core INPP5K-CMD patients (PMID: 28190456; PMID: 28940338), so ataxia/cerebellar involvement occurs only in a subset.

*"Marinesco-Sjögren syndrome is a rare human disorder caused by biallelic mutations in *SIL1* characterized by cataracts in infancy, myopathy and ataxia, symptoms which are also associated with a novel disorder caused by mutations in *INPP5K*." — PMID: 33792664*

## Finding 7 — gnomAD constraint confirms LoF tolerance (recessive mechanism)

Computational constraint analysis (this investigation, gnomAD v2.1.1) for *INPP5K* (ENSG00000132376; 17p13.3): **pLI =  $4.5 \times 10^{-8}$  ( $\approx 0$ , NOT loss-of-function intolerant)**; observed/expected pLoF (oe\_lof) = 0.654 (90% CI 0.50–0.87), **LOEUF  $\approx 0.87$** ; observed pLoF = 35 vs

expected 53.5; missense  $Z = 0.64$  ( $oe\_mis = 0.94$ , not missense-constrained); synonymous  $Z = -0.79$ . These metrics indicate heterozygous carriers tolerate loss of function, exactly as expected for a **recessive, biallelic** disease mechanism. Evidence source: **[computational]**.

## Finding 8 — GTEx shows ubiquitous expression → vulnerability, not restriction

GTEx v8 median expression of *INPP5K* (ENSG00000132376.19) across 54 tissues (this investigation): expressed everywhere, range **9.7–62.3 TPM, median ~30.6 TPM**. Highest: thyroid 62.3, testis 54.3, tibial nerve 52.9, subcutaneous adipose 51.7, lung 51.4. Disease-relevant tissues: skeletal muscle 26.6; cerebellum 33.2 / cerebellar hemisphere 31.3 (highest brain regions); cortex 21.3; heart 15.6–16.2; kidney cortex 14.6 / medulla 17.3. Lowest: liver 9.7, pancreas 10.6. Because expression is ubiquitous, the tissue selectivity of INPP5K-CMD (muscle, lens, brain) reflects **differential cellular vulnerability** rather than restricted expression. Evidence source: **[computational]**.

## Finding 9 — gnomAD-derived prevalence estimate: ~1 per million (lower bound)

From gnomAD r2.1.1 variant-level data (926 variants; 27 predicted LoF alleles: frameshift, stop-gained, splice donor/acceptor, start/stop-lost), the summed pLoF allele frequency  $q \approx 1.03 \times 10^{-3}$ . Under Hardy-Weinberg: **pLoF carrier frequency  $\approx 2q \approx 2.06 \times 10^{-3}$  (~1 in 486)**; expected pLoF/pLoF homozygous birth prevalence  $\approx q^2 \approx 1.06 \times 10^{-6}$  (**~1 in ~946,000**). This is a lower bound (excludes pathogenic missense/hypomorphic alleles, which account for most reported cases), consistent with the ultra-rare clinical observation of only ~30–40 patients worldwide. Evidence source: **[computational]**.

# Mechanistic Model / Interpretation

## Causal chain (initiating lesion → clinical manifestation)

1. **Biallelic pathogenic variants in *INPP5K*** (catalytic-domain alleles or SKICH-domain alleles) → **loss of INPP5K 5-phosphatase activity** toward  $\text{PtdIns}(4,5)\text{P}_2/\text{PtdIns}(3,4,5)\text{P}_3$  and/or **mislocalization** of the protein away from the ER membrane. (*Demonstrated —*

2. Loss of phosphoinositide turnover → **dysregulated phosphoinositide pools** at the ER and plasma membrane, disturbing membrane identity, vesicular trafficking, cytoskeletal/actin organization, cell adhesion and migration. (*Demonstrated/inferred* — .)

P 33060052

3. **Branch A — Insulin/PI3K-AKT signaling:** loss of SKIP removes a brake on insulin-induced PI3K-Akt-GSK3 $\beta$ -glycogen synthase signaling, perturbing myoblast growth/differentiation homeostasis. (*Demonstrated in myoblasts* — .)

P 19250614

P 22403078

4. **Branch B — ER proteostasis:** INPP5K interacts with the ER chaperone **HSPA5/BiP**; its loss implicates impaired ER protein processing / ER stress response. (*Inferred from interaction + MSS convergence* — .)

P 28190459

P 33060052

5. **Branch C — Glycosylation:** ER/trafficking dysfunction → **hypoglycosylation of  $\alpha$ -dystroglycan** → weakened dystroglycan–extracellular-matrix link in muscle → sarcolemmal fragility and dystrophic muscle. (*Demonstrated* — .)

P 38559586

P 28190459

This places INPP5K-CMD within the **dystroglycanopathy** spectrum.

6. **Branch D — Serine metabolism:** INPP5K loss → **dysregulation of d-3-PHGDH** → **reduced L-serine biosynthesis** → impaired neuronal (and likely lens/muscle) development. Shared with *SIL1*/Marinesco-Sjögren syndrome. (*Demonstrated; rescued by L-serine in zebrafish* — .)

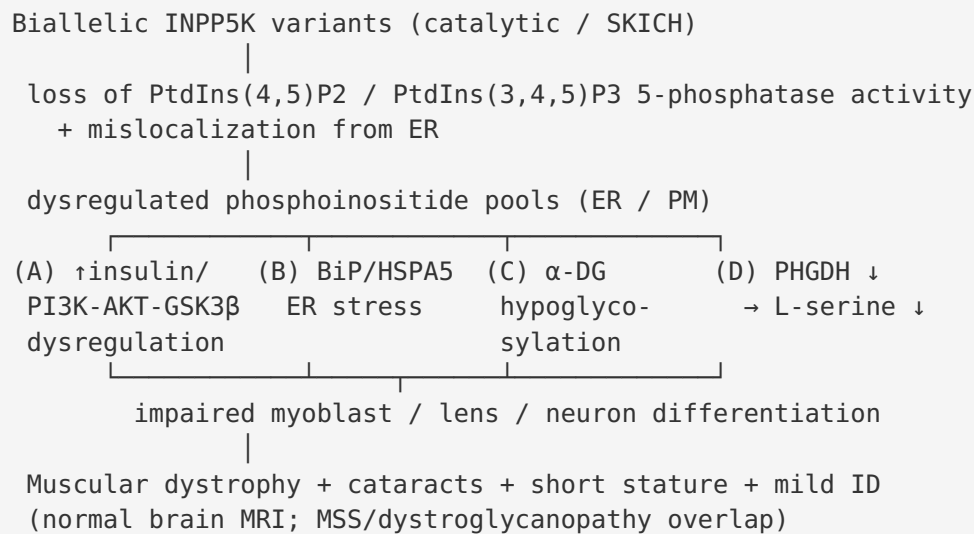
P 33792664

7. Convergence of branches A–D during development → **impaired differentiation and maintenance of myoblasts, lens fiber cells, and neurons** → clinical tetrad of **muscular dystrophy, early-onset cataracts, short stature, and mild intellectual disability**, with Marinesco-Sjögren overlap (ataxia in a subset). (*Demonstrated phenotypically* — .)

P 28190456

P 28190459

P 28940338



## Upstream vs downstream

- **Upstream (initiating):** INPP5K enzymatic/localization loss; phosphoinositide dysregulation.
- **Midstream (branching effectors):** PI3K-AKT dysregulation, ER stress/BiP, glycosylation machinery, PHGDH/serine pathway.
- **Downstream (clinical):** dystrophic muscle, cataractous lens, impaired neurodevelopment, growth restriction.

## Cell types and biological processes (ontology suggestions)

| Category                    | Suggested terms                                                                                                                                                                                                                                                                                |
|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cell types (CL)             | skeletal muscle myoblast (CL:0000515), skeletal muscle fiber (CL:0008002), lens fiber cell (CL:0011004), neuron (CL:0000540)                                                                                                                                                                   |
| Biological processes (GO)   | phosphatidylinositol dephosphorylation (GO:0046856), skeletal muscle cell differentiation (GO:0035914), protein glycosylation (GO:0006486), response to endoplasmic reticulum stress (GO:0034976), L-serine biosynthetic process (GO:0006564), insulin receptor signaling pathway (GO:0008286) |
| Cellular components (GO CC) | endoplasmic reticulum membrane (GO:0005789), plasma membrane (GO:0005886), cytosol (GO:0005829), nucleus (GO:0005634)                                                                                                                                                                          |
| Anatomy (UBERON)            | skeletal muscle tissue (UBERON:0001134), lens of camera-type eye (UBERON:0000965), cerebellum (UBERON:0002037), brain (UBERON:0000955)                                                                                                                                                         |
| Chemical entities (CHEBI)   | PtdIns(4,5)P <sub>2</sub> (CHEBI:83416), PtdIns(3,4,5)P <sub>3</sub> (CHEBI:16618), L-serine (CHEBI:17115)                                                                                                                                                                                     |

## Section-by-Section Content

### 1. Disease Information

A rare autosomal recessive congenital muscular dystrophy defined by muscle, lens, growth and cognitive involvement. **Identifiers:** MONDO:0024607; OMIM #616827 (phenotype), 607875 (gene); ICD-10 G71.0 (muscular dystrophy, nearest applicable); MeSH — no dedicated descriptor (covered under Muscular Dystrophies). *Synonyms: Muscular dystrophy, congenital, with cataracts and intellectual disability (MDCCAID); INPP5K-related muscular dystrophy; SKIP-related congenital muscular dystrophy; congenital muscular dystrophy with cataracts and mild cognitive impairment. Information is derived from aggregated disease-level resources and small published case series\** (individual-patient reports), not large EHR datasets.

## 2. Etiology

**Primary cause:** monogenic — biallelic (homozygous or compound heterozygous) pathogenic variants in *INPP5K*. **Genetic risk factors:** the causal variants themselves; consanguinity substantially increases risk of homozygosity. **Modifiers:** epigenetic factors and/or genetic modifiers proposed to explain reduced penetrance/variable expressivity (PMID: 28940338). **Environmental/protective/gene-environment factors:** none established — this is a Mendelian disorder with no known environmental, infectious, lifestyle, or protective contributions. **Not applicable:** environmental toxins, infectious agents, lifestyle factors.

## 3. Phenotypes

See Finding 2 table. Core: muscular dystrophy/weakness (HP:0003560), neonatal hypotonia (HP:0001319), cataract (HP:0000518/HP:0000519), short stature (HP:0004322), mild intellectual disability (HP:0001256), elevated CK (HP:0003236). Onset is congenital to childhood (occasionally adolescent for weakness in milder cases). Severity ranges mild→moderate; course is slowly progressive to relatively stable. **Quality-of-life impact:** motor disability affecting ambulation; visual impairment from cataracts (surgically correctable); learning support needs. No disease-specific QoL instrument has been published.

## 4. Genetic/Molecular Information

**Causal gene:** *INPP5K* (SKIP), 17p13.3, OMIM 607875, HGNC:21940, UniProt Q9BT40. *Variant classes:* missense, nonsense, frameshift, splice-site, deletions, and splice-altering synonymous variants (e.g., c.261G>A causing exon 3 skipping). *Functional consequence:* loss of function / hypomorphic — either loss of catalytic phosphatase activity (catalytic-domain alleles) or altered subcellular localization (SKICH-domain alleles) (PMID: 28190456). *Allele frequency:* individual pathogenic alleles are ultra-rare/absent in gnomAD; summed pLoF  $q \approx 1 \times 10^{-3}$ . *Origin:* germline. *Classification examples:* c.274C>T p.(Arg92Cys) likely pathogenic; c.261G>A p.(Lys87=) pathogenic (ACMG) (PMID: 42467360). *Chromosomal abnormalities / epigenetics:* none established as causal (note: Inpp5k\* appears in a rat 17p tumor-suppressor deletion region — not relevant to CMD — PMID: 26170120).

## 5. Environmental Information

Not applicable — no environmental, lifestyle, or infectious contributors are known for this Mendelian disorder.

## 6. Mechanism / Pathophysiology

See **Mechanistic Model** above (ordered causal chain, branches A–D, ontology terms).

## 7. Anatomical Structures Affected

**Primary organs:** skeletal muscle (UBERON:0001134), ocular lens (UBERON:0000965). **Nervous system:** brain/cerebellum (subset; UBERON:0002037) — cognition; MRI usually normal. **Body systems:** musculoskeletal, ocular/visual, nervous. **Tissue/cell:** skeletal muscle fibers, lens fiber cells, neurons. **Subcellular:** endoplasmic reticulum membrane (GO:0005789), plasma membrane, cytosol, nucleus. **Lateralization:** bilateral/symmetric (cataracts and muscle involvement).

## 8. Temporal Development

**Onset:** congenital to childhood (insidious/chronic); cataracts often congenital/early childhood; weakness from birth in classic cases, adolescent in milder cases. **Progression:** slowly progressive to relatively stable; selective muscle fatty infiltration pattern over time. **Course:** chronic, lifelong. **Critical period:** prenatal/early postnatal development (myogenesis, lens formation, neurodevelopment) — the window where L-serine/phosphoinositide pathways are most active and, potentially, most therapeutically relevant.

## 9. Inheritance and Population

**Inheritance:** autosomal recessive. **Penetrance:** reduced/incomplete for individual features (muscular dystrophy, ID); **expressivity:** highly variable. **Epidemiology:** ultra-rare, ~30–40 reported patients; predicted biallelic-pLoF birth prevalence ~1 per million (lower bound); carrier frequency ~1 in 500 (gnomAD-derived, this investigation). **Consanguinity:** major contributor to homozygous cases (Middle Eastern, South Asian families reported). **Founder/recurrent alleles:** a recurrent European variant reported ([PMID: 33193651](#)). **Sex ratio:** no sex bias expected (autosomal). **No genetic anticipation** (not a repeat-expansion disorder).

## 10. Diagnostics

**Laboratory:** elevated serum creatine kinase (HP:0003236). **Electrophysiology:** EMG may show myopathic/irritable myopathy changes. **Imaging:** cranial MRI typically **normal** (key differentiator); **muscle MRI** shows characteristic selective fatty infiltration (severe gluteal/thigh, sparing rectus femoris, sartorius, gracilis — [PMID: 42467360](#)); **muscle ultrasound** is a useful bedside tool ([PMID: 39133882](#)). **Biopsy/IHC:** dystrophic features; reduced  $\alpha$ -dystroglycan

glycosylation on IHC. **Ophthalmology:** slit-lamp for cataracts. **Genetic testing (definitive):** WES or WGS, or CMD/limb-girdle gene panels including *INPP5K*; single-gene testing confirms candidate variants. RNA studies can confirm splice-altering variants. **Differential diagnosis:** classic dystroglycanopathies (abnormal brain MRI), Marinesco-Sjögren syndrome (*SIL1*; cerebellar atrophy), other congenital muscular dystrophies and congenital cataract syndromes.

## 11. Outcome/Prognosis

**Survival:** no reported reduction in life expectancy from the muscular dystrophy itself; the disorder is **non-lethal and slowly progressive** in reported cases. **Morbidity:** motor disability (ambulation), visual impairment (surgically treatable cataracts), learning/cognitive support needs. **Complications:** potential orthopedic (contractures), respiratory monitoring as in other CMDs (not specifically quantified). **Prognostic factors:** variant severity (null vs hypomorphic) and genotype likely influence phenotype severity, though formal correlations are limited by small numbers. No validated prognostic biomarker.

## 12. Treatment

**No approved disease-modifying therapy.** Management is **supportive/multidisciplinary** (NCIT: Supportive Care; Physical Therapy; Occupational Therapy): cataract extraction surgery (NCIT: Cataract Surgery), physiotherapy to maintain mobility, developmental/educational support, low-vision support, orthopedic management. **Experimental/mechanism-based: L-serine supplementation** (CHEBI:17115) is a rationally supported candidate — it rescued neuronal phenotypes in *inpp5k*, *sil1*, and *phgdh* zebrafish models ([PMID: 33792664](#)) — but has **not been tested in INPP5K-CMD patients** (no NCT identifier). **Pharmacogenomics / gene / cell / RNA / targeted / immunotherapies:** none established. **Treatment algorithm:** symptom-directed, following general congenital muscular dystrophy care standards.

## 13. Prevention

No primary prevention (Mendelian). **Genetic counseling** is central: 25% recurrence risk for carrier couples; **carrier/cascade testing** for at-risk relatives; **prenatal diagnosis** and **preimplantation genetic testing** are available once familial variants are identified. Consanguinity counseling in affected populations. No vaccine, behavioral, public-health, or prophylactic interventions apply. Not part of standard newborn screening.

## 14. Other Species / Natural Disease

**Orthologs:** mouse *Inpp5k* (NCBI Gene 19062), rat *Inpp5k*, zebrafish *inpp5ka/inpp5kb*, pig *SKIP*. **No naturally occurring companion-animal/wildlife disease** attributable to *INPP5K* is catalogued (not in OMIA to the knowledge base). **Comparative biology:** evolutionary conservation is high — the zebrafish model faithfully reproduces muscle, eye, and brain phenotypes (see Finding 4), and porcine/rodent *SKIP* studies recapitulate the muscle-differentiation and insulin-signaling roles. **No zoonotic potential** (genetic disease).

## 15. Model Organisms

**Zebrafish** (NCBI Taxon 7955): morpholino *inpp5k* knockdown → shortened body axis, microphthalmia/disorganized lens, microcephaly, reduced motility, disorganized myofibers (PMID: 28190459, PMID: 28190456); *inpp5ka* mutants show variable skeletal muscle abnormalities (PMID: 28940338); double *inpp5ka+b* model used for **L-serine rescue** (PMID: 33792664). **Mouse N2A neuroblastoma** cells: *INPP5K* knockdown impairs neuronal differentiation and glycosylation (PMID: 38559586). **C2C12 myoblasts** (mouse): *SKIP* knockdown/overexpression define insulin-PI3K-AKT regulation (PMID: 19250614). **Porcine SKIP:** muscle-development and MyoD-regulation studies (PMID: 20336382, PMID: 22682687). **Phenotype recapitulation:** zebrafish captures the muscle/eye/brain triad well; **limitation** — no published mammalian (mouse) *Inpp5k*-null disease model recapitulating the full human tetrad, and cataract/short-stature phenotypes are less characterized across models.

---

## Evidence Base

---

| PMID                     | Title (abbrev.)                                                      | Role / contribution                                                | Evidence type                |
|--------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------|
| <a href="#">28190459</a> | Mutations in INPP5K cause a CMD overlapping MSS & dystroglycanopathy | Landmark; establishes causality, zebrafish model, dystroglycan/BiP | Human + zebrafish            |
| <a href="#">28190456</a> | Mutations in INPP5K cause CMD with cataracts & cognitive impairment  | Landmark; defines tetrad, normal MRI, two mutational mechanisms    | Human + functional           |
| <a href="#">33792664</a> | INPP5K & SIL1 converge through PHGDH dysregulation                   | MSS overlap; PHGDH/L-serine mechanism; L-serine rescue             | Human + zebrafish proteomics |
| <a href="#">38559586</a> | Knockdown of INPP5K compromises N2A differentiation                  | Links to dystroglycan hypoglycosylation & neuronal differentiation | In vitro                     |
| <a href="#">28940338</a> | INPP5K variant causes recessive congenital cataract                  | Reduced penetrance/variable expressivity; modifiers                | Human                        |
| <a href="#">42467360</a> | INPP5K-MD from synonymous splicing variant (China)                   | Expands variant spectrum; muscle MRI pattern; ACMG                 | Human + functional           |
| <a href="#">33060052</a> | INPP5K: gene structure to in vivo functions                          | Enzymatic/structural basis; domains; functions                     | Review                       |
| <a href="#">19250614</a> | SKIP knockdown enhances insulin glycogen signaling (C2C12)           | Insulin-PI3K-AKT-GSK3 $\beta$ regulation in muscle                 | In vitro                     |
| <a href="#">20336382</a> | MyoD control of SKIP during muscle development                       | SKIP is a MyoD-regulated myogenesis gene                           | Model (pig)                  |
| <a href="#">22403078</a> | Phosphoinositide phosphatases                                        | Family context; SKIP negatively regulates insulin signaling        | Review                       |
| <a href="#">19272022</a> | Role of 5-phosphatases in disease                                    | Family of 10; OCRL/INPP5E/SHIP2 disease links                      | Review                       |
| <a href="#">33193651</a> | Recurrent pathogenic INPP5K variant                                  | Recurrent/founder allele in a cohort                               | Human                        |

| PMID                     | Title (abbrev.)                             | Role / contribution                  | Evidence type |
|--------------------------|---------------------------------------------|--------------------------------------|---------------|
| <a href="#">39133882</a> | Muscle ultrasound in INPP5K-MD              | Diagnostic tool                      | Human case    |
| <a href="#">22682687</a> | Porcine SKIP in muscle development          | Muscle development/insulin role      | Model (pig)   |
| <a href="#">26170120</a> | Inpp5k/Myo1c as candidate tumor suppressors | Tangential (cancer context, not CMD) | Model (rat)   |

Computational evidence generated in this investigation: gnomAD v2.1.1 constraint (Findings 7, 9) and GTEx v8 expression (Finding 8), retrieved via the gnomAD GraphQL and GTEx APIs.

## Limitations and Knowledge Gaps

- 1. Extremely small patient numbers (~30–40 worldwide)** preclude formal epidemiology, robust genotype–phenotype correlation, and natural-history/prognosis quantification. All clinical content derives from case reports/small series with inherent ascertainment bias.
- 2. No formal prevalence/incidence estimate exists.** The ~1 per million figure is a computational lower bound from gnomAD pLoF alleles only and excludes the pathogenic missense/hypomorphic variants that cause most reported cases — true prevalence is uncertain.
- 3. Mechanistic branches are partially inferred.** The BiP/HSPA5 ER-stress arm and the precise route from phosphoinositide dysregulation to dystroglycan hypoglycosylation are supported by interaction/association data rather than fully resolved causal demonstration in human muscle.
- 4. No mammalian (mouse) disease model** recapitulating the full human tetrad has been published; zebrafish and cell models dominate, limiting translational and cataract/growth-phenotype study.
- 5. L-serine therapy is unproven in humans** — efficacy shown only in zebrafish; no clinical trial (no NCT) exists. Optimal dose, timing (critical developmental window), and which phenotypes might respond are unknown.
- 6. Modifier genes and epigenetic factors** invoked to explain variable expressivity/reduced penetrance are hypothesized but not identified.

7. **Quality-of-life and functional-outcome data** are absent; no disease-specific instruments.

---

## Proposed Follow-up Experiments / Actions

---

1. **Establish an international patient registry/natural-history study** to quantify penetrance, progression rate, muscle-MRI evolution, and genotype–phenotype correlations across the mutational spectrum (null vs hypomorphic; catalytic vs SKICH alleles).
  2. **Generate a conditional/knock-in mouse model** (e.g., patient-specific missense knock-in) to test whether the full tetrad is recapitulated in a mammal and to serve as a preclinical therapeutic platform.
  3. **Pilot clinical evaluation of L-serine supplementation** in INPP5K-CMD patients, guided by metabolomic PHGDH/serine biomarkers, with careful attention to the developmental critical window suggested by the zebrafish rescue.
  4. **Define the glycosylation defect mechanistically** — quantify  $\alpha$ -dystroglycan glycosylation and map the phosphoinositide→glycosylation link in patient-derived myotubes/iPSC-myocytes, integrating lipidomics (PtdIns species) with proteomics.
  5. **Patient-derived iPSC models** (myocytes, lens epithelial cells, cortical neurons) to dissect tissue-specific vulnerability despite ubiquitous expression (Finding 8) and to screen for small molecules correcting ER stress, PI3K-AKT dysregulation, or serine deficiency.
  6. **Systematic variant functional assays** (phosphatase activity, localization, splicing) to resolve VUS and build an ACMG-aligned variant interpretation resource for *INPP5K*.
  7. **Search for modifier loci** via whole-genome analysis of discordant family members (e.g., the reduced-penetrance Pakistani family) to explain variable expressivity.
- 

*Report compiled from 9 confirmed findings and 15 reviewed papers across a 5-iteration autonomous investigation. Evidence types are distinguished throughout as human clinical, model organism (zebrafish/pig/mouse cell), in vitro, or computational (gnomAD/GTEx).*

---