SRD5A3-Congenital Disorder of Glycosylation (SRD5A3-CDG): A Comprehensive Disease Characterization Report

Category: Mendelian (autosomal recessive inborn error of metabolism) **Compiled:** 2026-09-01 | Evidence base: primary literature (PMIDs cited inline)

Summary

SRD5A3-Congenital Disorder of Glycosylation (SRD5A3-CDG; OMIM #612379; CDG type Iq; Orphanet ORPHA:79320) is a rare autosomal recessive inborn error of metabolism caused by biallelic loss-of-function variants in *SRD5A3* (steroid 5α-reductase type 3; chromosome 4q12; HGNC:24420; OMIM *611715). The gene encodes polyprenol reductase, the enzyme that catalyzes the final, committed step of dolichol biosynthesis — reduction of the α-isoprene unit of polyprenol to form dolichol (PMID: 20637498). Because dolichol is the obligate lipid carrier for the dolichol-linked oligosaccharide (LLO) precursor of protein N-glycosylation, and also anchors glycans used in O-/C-mannosylation and glycosylphosphatidylinositol (GPI) anchor biosynthesis, enzyme deficiency produces a CDG type I** biochemical defect (hypoglycosylation of nascent glycoproteins) that branches to affect multiple glycosylation pathways at the endoplasmic reticulum (ER) membrane.

Clinically, SRD5A3-CDG is a **congenital multisystem neuro-ophthalmologic-dermatologic disorder**. Its consistent core features are intellectual disability/psychomotor delay, muscular hypotonia, cerebellar ataxia with cerebellar hypoplasia/atrophy, and a characteristic ocular spectrum (congenital nystagmus, optic disc pallor/optic atrophy, early-onset retinal dystrophy, ocular coloboma, cataract), frequently accompanied by ichthyosiform skin/chronic dermatitis. The historically separate **Kahrizi syndrome** (OMIM 612713: intellectual disability, coloboma, cataract, kyphosis) is allelic — indeed the same disorder (PMID: 20700148). Adult-onset/progressive features include kyphosis/scoliosis, retinitis pigmentosa, and cataracts (PMID: 27480077).

The disorder is **ultrarare**, with roughly 60 cases reported worldwide and approximately 23 distinct pathogenic variants described as of 2022. Diagnosis relies on exome/genome sequencing (including intragenic copy-number analysis) supported by a CDG-I serum transferrin pattern and biochemical demonstration of an elevated polyprenol/dolichol ratio. **No disease-modifying therapy exists**; management is symptomatic and multidisciplinary. Repurposing of the HMG-CoA reductase inhibitor atorvastatin and dietary dolichol supplementation remain experimental. This report synthesizes eight confirmed findings across 35 reviewed papers to populate the disease knowledge-base template.

Key Findings

Finding 1 — Genetic cause: biallelic loss-of-function *SRD5A3* variants encoding polyprenol reductase

SRD5A3 (chromosome 4q12; HGNC:24420; OMIM *611715) encodes polyprenol reductase, which reduces the α-isoprene unit of polyprenol to form dolichol. Dolichol is the obligate lipid carrier for the dolichol-linked oligosaccharide precursor used in protein N-glycosylation, O-/C-mannosylation, and GPI-anchor synthesis. Biallelic pathogenic variants cause SRD5A3-CDG (a CDG type I disorder; OMIM #612379), inherited in an autosomal recessive manner. The seminal functional study established both gene function and disease causation:* "We found that SRD5A3 is necessary for the reduction of the alpha-isoprene unit of polyprenols to form dolichols, required for synthesis of dolichol-linked monosaccharides, and the oligosaccharide precursor used for N-glycosylation"* (PMID: 20637498).

Notably, the same study observed residual dolichol in enzyme-depleted cells: *"The presence of residual dolichol in cells depleted for this enzyme suggests the existence of an unexpected alternative pathway for dolichol de novo biosynthesis"* (PMID: 20637498). This alternative/"detour" pathway — recently shown to be evolutionarily conserved in budding yeast (PMID: 42201967) — explains why patients retain partial glycosylation capacity despite null variants and likely accounts for survival compatible with life in this disorder.

Finding 2 — Core clinical phenotype: neurodevelopmental, ophthalmologic, cerebellar, and cutaneous involvement

Across independent patient cohorts, SRD5A3-CDG presents a recognizable multisystem picture: intellectual disability/psychomotor delay, muscular hypotonia, cerebellar ataxia with cerebellar hypoplasia/atrophy, congenital nystagmus, optic disc pallor/optic atrophy, early-onset retinal dystrophy, ocular coloboma, cataract, and ichthyosiform skin/chronic dermatitis. A concise clinical summary describes *"a severe metabolic disease manifesting as muscle hypotonia, developmental delay, cerebellar ataxia and ocular symptoms; typically, nystagmus and optic disc pallor"* (PMID: 31638560).

The **ocular phenotype** is a prominent and often presenting feature, with *"early-onset retinal dystrophy as a primary manifestation"* (PMID: 28253385). The allelic **Kahrizi syndrome** highlights the coloboma-cataract-kyphosis axis: *"a novel syndrome consisting of mental retardation, coloboma, cataract and kyphosis (Kahrizi syndrome, OMIM 612713)"* (PMID: 20700148). Phenotypic diversity is real: monozygotic twins have been reported with early-infancy generalized tonic-clonic seizures (a less common feature) yet entirely normal brain MRI at 20 months, demonstrating that the characteristic cerebellar structural anomalies may be absent early in life (PMID: 41769439).

Suggested HPO terms: HP:0001249 (Intellectual disability), HP:0001252 (Hypotonia), HP:0001251 (Ataxia), HP:0001321 (Cerebellar hypoplasia), HP:0000639 (Nystagmus), HP:0000648 (Optic atrophy), HP:0000556 (Retinal dystrophy), HP:0000589 (Coloboma), HP:0000518 (Cataract), HP:0008064 (Ichthyosis), HP:0002650 (Scoliosis), HP:0002808 (Kyphosis), HP:0001250 (Seizure).

Finding 3 — Biochemical signature: extensive serum hypoglycosylation, elevated polyprenol/dolichol ratio, CDG-I transferrin pattern

Patient fibroblasts exhibit a **high polyprenol/dolichol ratio with normal dolichol amounts**, the biochemical fingerprint of the enzyme defect: *"Quantification of dolichol and unreduced polyprenol in the patient's fibroblasts demonstrated a high polyprenol/dolichol ratio with normal amounts of dolichol"* (PMID: 22304929). Serum transferrin isoelectric focusing shows a **CDG type I** pattern, though a caveat exists — up to ~70% of transferrin may be correctly glycosylated in some patients, so screening can be falsely reassuring, and transferrin protein variants can further confound interpretation (as documented in PMM2-CDG, PMID: 37876147).

Quantitative serum N-glycoproteomics reveals the breadth of the defect: *"Extensive hypoglycosylation of serum proteins was observed in patients, with 245 of 291 altered glycopeptides decreased in SRD5A3-CDG"* (PMID: 41732066), affecting haptoglobin, plasma serine protease inhibitor, alpha-1-B glycoprotein, alpha-2-macroglobulin, ceruloplasmin, and albumin (including at non-canonical sites). Albumin-derived glycopeptides are emerging as diagnostic biomarkers across CDG subtypes including SRD5A3-CDG (PMID: 41713138). Molecular diagnosis is confirmed by exome/genome sequencing **with intragenic copy-number analysis**, because structural variants occur: *"we identified as a second compound heterozygous variant a previously not reported tandem duplication of exons 2-4 in SRD5A3"* (PMID: 35339718).

Finding 4 — No disease-modifying therapy; symptomatic management with atorvastatin repurposing under investigation

With ~60 reported cases, treatment is limited to **symptomatic/supportive management**: developmental therapies, ophthalmologic and orthopedic care, and seizure control. A recent study developed the first high-throughput disease models and reported repurposing of the HMG-CoA reductase inhibitor **atorvastatin** as an experimental therapeutic strategy: *"Approximately 60 cases have been reported, with treatment limited to symptomatic management"* (PMID: 41648237). Dietary **dolichol supplementation** has been proposed conceptually, supported by plant polyprenol-reductase rescue experiments (Finding 5). A broad 2024 CDG treatment overview reinforces that most CDG remain symptomatically managed: *"Mostly, we are only able to manage the disease symptoms rather than to address the underlying cause"* (PMID: 39236565), while noting that *"Innovative therapies, targeting both the root cause and resulting manifestations, have transitioned from the research stage to practical application"* for some subtypes (e.g., dietary sugar therapies in MPI-, PGM1-, and PMM2-CDG).

Finding 5 — Evolutionary conservation: plant/yeast models recapitulate the defect and dolichol rescues it

The polyprenol-to-dolichol reduction step is deeply conserved. *Arabidopsis thaliana* orthologs PPRD1 and PPRD2 encode polyprenol reductases: *"which are orthologous to human SRD5A3 (steroid 5α reductase type 3) and encode polyprenol reductases responsible for conversion of polyprenol to dolichol in Arabidopsis thaliana"* (PMID: 26628744). PPRD2 deficiency is lethal (male sterility) and is **partially rescued by dolichol**: *"Shortage of dolichol in PPRD2-deficient cells is partially rescued by PPRD1 overexpression or by supplementation with dolichol"* (PMID: 26628744), implicating impaired protein glycosylation as the major underlying factor. The

conserved dolichol biosynthesis "detour" pathway in budding yeast (PMID: 42201967) provides an additional tractable model system. These conserved systems provide the mechanistic rationale for dietary dolichol supplementation as a conceptual therapeutic avenue.

Finding 6 — Ultrarare disorder with variable expressivity, adult-onset progression, and founder alleles

Fewer than ~60 cases have been reported worldwide, with ~23 distinct variants known by 2022: *"So far, only 23 distinct mutations were described"* (PMID: 35339718). Inheritance is autosomal recessive with high representation of **consanguineous families** and population **founder alleles** (e.g., p.Gln96delinsX in Baluchi/South Asian families). Expressivity is variable even for recurrent alleles: *"Homozygosity for the SRDA3 deletion p.Gln96delinsX is not always associated with ocular coloboma"* (PMID: 30019980). Comparison of children and adults with *SRD5A3* mutations delineated progressive/adult-onset features: *"allowing us to delineate the features that may develop over time with this disorder including kyphosis, retinitis pigmentosa, and cataracts"* (PMID: 27480077). In the 280-patient FCDGC natural history cohort, dolichol-metabolism disorders (which include SRD5A3-CDG) comprised ~5% of participants (PMID: 38959600).

Finding 7 — Mechanism: dolichol deficiency impairs multiple ER glycosylation pathways

SRD5A3-derived dolichol is required for synthesis of dolichol-linked monosaccharides and the oligosaccharide precursor (**Glc3Man9GlcNAc2-PP-dolichol**) assembled in the ER during the dolichol cycle: *"required for synthesis of dolichol-linked monosaccharides, and the oligosaccharide precursor used for N-glycosylation"* (PMID: 20637498). Dolichyl-phosphate (Dol-P) is a **rate-limiting intermediate** of N-glycosylation and is recycled to the cytoplasmic ER leaflet after cleavage of dolichyl pyrophosphate: *"During protein N-glycosylation, dolichyl pyrophosphate (Dol-P-P) is discharged in the lumenal monolayer of the endoplasmic reticulum (ER)"* (PMID: 18077451). Because dolichol also anchors glycans in O-/C-mannosylation and GPI-anchor biosynthesis, the deficiency produces a CDG type I biochemical defect (hypoglycosylation of nascent proteins) that **branches** to impair those pathways as well.

Finding 8 — CDG therapy is largely symptomatic; no established SRD5A3-specific therapy and no isolated mouse disease model

A 2024 overview (Quelhas & Jaeken) confirms that available CDG treatment options remain limited and mostly symptomatic, though targeted root-cause therapies have recently reached practice for some subtypes (PMID: 39236565). For SRD5A3-CDG specifically, no disease-specific therapy is established; atorvastatin repurposing is experimental. A key **model-organism gap** exists: no isolated *Srd5a3*-knockout mouse disease model has been characterized — a mouse ~1.2 Mb 5qC3.3 deletion encompassing *Srd5a3* caused peri-implantation lethality attributable to *Exoc1*, not *Srd5a3*: *"deletion of a > 1.2-Mb genomic region containing nine genes (Kit, Kdr, Srd5a3, Tmeme165, Clock, Pdcl2, Nmu, Exoc1, and Cep135)"* (PMID: 26346620).

Detailed Section-by-Section Report

1. Disease Information

Overview. SRD5A3-CDG is an autosomal recessive congenital disorder of glycosylation of the dolichol-metabolism subgroup. Dysfunction of polyprenol reductase blocks the terminal step of dolichol synthesis, reducing availability of the LLO precursor required for protein N-glycosylation and impairing other dolichol-dependent glycan pathways, producing a congenital multisystem disorder dominated by neurodevelopmental, cerebellar, ophthalmologic, and cutaneous features.

Key identifiers: - **OMIM (disease):** #612379 (Congenital disorder of glycosylation, type Iq) - **OMIM (allelic):** #612713 (Kahrizi syndrome) - **OMIM (gene):** *611715 (*SRD5A3*) - Orphanet: ORPHA:79320 (SRD5A3-CDG) - Gene / HGNC:* SRD5A3 */ HGNC:24420 - Chromosome: 4q12 - Suggested MONDO: MONDO:0012997 (congenital disorder of glycosylation, type Iq) — verify against current MONDO release - ICD-10: E77.8 (other disorders of glycoprotein metabolism); ICD-11: 5C51.1 (disorders of protein glycosylation) — subtype-level codes are not disease-specific - MeSH:** Congenital Disorders of Glycosylation (D018981) — no SRD5A3-specific descriptor

Synonyms / alternative names: SRD5A3-CDG; CDG type Iq (CDG-Iq); steroid 5α-reductase type 3 deficiency; polyprenol reductase deficiency; Kahrizi syndrome (allelic); congenital disorder of glycosylation with intellectual disability, coloboma, cataract and kyphosis.

Information source type. Disease-level knowledge derives predominantly from **aggregated disease-level resources** (OMIM, Orphanet) and from **published individual/small-cohort case reports and case series** plus the multicenter FCDGC natural history study — not from large EHR datasets, consistent with ultrarare-disease evidence.

2. Etiology

Causal factors — genetic. SRD5A3-CDG is a monogenic disorder caused by **biallelic (homozygous or compound heterozygous) loss-of-function variants in *SRD5A3*** (PMID: 20637498). There is no environmental or infectious cause.

Genetic risk factors. The only risk factor is inheritance of two pathogenic *SRD5A3* alleles. **Consanguinity** substantially increases risk (many cases arise in consanguineous families), and **founder alleles** exist in specific populations (e.g., p.Gln96delinsX in Baluchi/South Asian families; PMID: 30019980).

Environmental risk factors / protective factors / gene-environment interactions. Not applicable — as a Mendelian metabolic disorder, no established environmental risk, protective, or gene-environment interaction factors have been reported. No genetic modifier or protective alleles have been defined, though the conserved dolichol "detour"/alternative biosynthesis pathway (PMID: 20637498; PMID: 42201967) likely modulates residual glycosylation capacity and phenotypic severity.

3. Phenotypes

Phenotype	Type	Onset	Frequency	Suggested HPO
Intellectual disability / psychomotor delay	Cognitive/ developmental	Congenital/infantile	Very frequent (near-universal)	HP:0001249
Muscular hypotonia	Clinical sign	Neonatal/infantile	Very frequent	HP:0001252
Cerebellar ataxia	Neurological sign	Infantile/childhood	Frequent	HP:0001251
Cerebellar hypoplasia/ atrophy	Imaging/ structural	Congenital (may be absent early)	Frequent	HP:0001321 / HP:0001272
Congenital nystagmus	Ophthalmologic sign	Congenital/infantile	Frequent	HP:0000639
Optic disc pallor / optic atrophy	Ophthalmologic sign	Infantile	Frequent	HP:0000648
Early-onset retinal dystrophy	Ophthalmologic	Early childhood	Frequent (can be presenting)	HP:0000556
Ocular coloboma	Physical malformation	Congenital	Variable	HP:0000589
Cataract	Ophthalmologic	Congenital→adult	Variable/ progressive	HP:0000518
Ichthyosiform skin / chronic dermatitis	Cutaneous	Infantile	Frequent	HP:0008064
Kyphosis / scoliosis	Skeletal	Adult-onset/ progressive	Variable	HP:0002808 / HP:0002650
Retinitis pigmentosa	Ophthalmologic	Adult-onset/ progressive	Variable	HP:0000510
	Neurological		Less common	HP:0001250

Phenotype	Type	Onset	Frequency	Suggested HPO
Seizures (incl. GTCS)		Variable (can be early)		

Onset, severity, progression. Most features are **congenital or infantile-onset**. Severity is **variable** (mild to severe), and expressivity varies even for identical genotypes (PMID: 30019980). The neurodevelopmental deficit is generally **stable/non-degenerative** in its cognitive component, while several features are **progressive** (kyphosis, retinitis pigmentosa, cataracts; PMID: 27480077). Structural cerebellar findings may be **absent in the first years** despite prominent neurological symptoms (PMID: 41769439).

Quality-of-life impact. No disease-specific EQ-5D/SF-36/PROMIS data exist for SRD5A3-CDG. By extrapolation from CDG cohorts, the combination of intellectual disability, ataxia, and visual impairment causes substantial dependency and impaired daily functioning; the FCDGC cohort found 100% of participants had developmental differences and high burdens of neurologic, GI/liver, and musculoskeletal involvement (PMID: 38959600).

4. Genetic / Molecular Information

Causal gene. *SRD5A3* (HGNC:24420; OMIM *611715; chromosome 4q12), encoding polyprenol reductase (UniProt Q9H8P0). Loss of function is the disease mechanism (PMID: 20637498).

Pathogenic variants. Approximately **23 distinct variants** were described by 2022 (PMID: 35339718). Reported variant classes include: - **Frameshift** (e.g., the homozygous frameshift in the original Kahrizi-syndrome family; PMID: 20700148) - **Nonsense** (e.g., c.57G>A, p.Trp19Ter, ACMG-pathogenic; PMID: 41769439) - **Missense** (e.g., c.509A>G, p.Tyr170Cys, likely pathogenic; PMID: 41667393) - **In-frame deletion/indel** founder allele (p.Gln96delinsX; PMID: 30019980) - **Intragenic structural variants** — a tandem duplication of exons 2–4 (PMID: 35339718)

ACMG/AMP classification. Reported variants are predominantly **pathogenic or likely pathogenic**, consistent with the broader FCDGC cohort in which most CDG variants were classified pathogenic/likely pathogenic (PMID: 38959600). **Allele frequencies** in gnomAD are very low (consistent with an ultrarare recessive disorder); founder alleles are enriched in specific populations.

Origin and functional consequence. Variants are **germline**; there is no somatic component. Functional consequence is **loss of function** (reduced/absent polyprenol reductase activity → impaired dolichol synthesis).

Modifier genes / epigenetics / chromosomal abnormalities. No established modifier genes or epigenetic mechanisms have been reported. The conserved alternative dolichol biosynthesis pathway is a candidate biological modifier of residual glycosylation (PMID: 20637498; PMID: 42201967). No characteristic large-scale chromosomal abnormalities are associated, though intragenic copy-number changes must be sought (PMID: 35339718).

5. Environmental Information

Not applicable. SRD5A3-CDG is a purely genetic Mendelian disorder. No environmental toxins, lifestyle factors, or infectious agents cause or trigger the disease. (Of note, the DPMS/dolichol-phosphate-mannose pathway is a host dependency factor for flaviviruses such as dengue/Zika PMID: 31915280, but this concerns viral biology, not SRD5A3-CDG etiology.)

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. **Biallelic loss-of-function variants in *SRD5A3*** reduce/abolish **polyprenol reductase** activity. *(demonstrated; PMID: 20637498)*
2. Loss of enzyme activity **prevents reduction of the α-isoprene unit of polyprenol**, so polyprenol accumulates and **dolichol formation is impaired** → elevated polyprenol/dolichol ratio in cells. *(demonstrated; PMID: 22304929)*
3. Reduced dolichol/dolichyl-phosphate **limits synthesis of dolichol-linked monosaccharides and the LLO precursor Glc3Man9GlcNAc2-PP-dolichol** in the ER (Dol-P is rate-limiting). *(demonstrated; PMID: 20637498; PMID: 18077451)*
4. Deficient LLO precursor **leads to protein N-hypoglycosylation** (a CDG type I defect) — extensive across serum glycoproteins. *(demonstrated; PMID: 41732066)*
5. **Branch 4a:** Reduced dolichol-anchored glycan donors also **impair O-/C-mannosylation and GPI-anchor biosynthesis**. *(inferred from shared dolichol dependency; PMID: 20637498; PMID: 40902550)*
6. Widespread hypoglycosylation **disrupts glycoprotein folding, stability, trafficking, and function** across many tissues. *(inferred; general glycoprotein quality-control biology, PMID: 10794707)*
7. Tissue-level dysfunction — most sensitively in **developing brain/cerebellum, retina/eye, and skin** — **results in** the clinical phenotype: intellectual disability, hypotonia, cerebellar ataxia/hypoplasia, the ocular spectrum, and ichthyosis. *(clinical correlation; PMID: 31638560)*

8. **Branch 6a (residual pathway):** A conserved alternative dolichol biosynthesis pathway supplies residual dolichol, **mitigating severity** and explaining survival and partial glycosylation. *(inferred/demonstrated in models; PMID: 20637498; PMID: 42201967)*

ASCII pathway diagram:

```
SRD5A3 biallelic LoF
       │ (loss of polyprenol reductase activity)
       ▼
Polyprenol NOT reduced ──► ↑ polyprenol/dolichol ratio
       │ (dolichol/Dol-P deficient)
       ▼
↓ Dolichol-linked monosaccharides + LLO (Glc3Man9GlcNAc2-PP-Dol)  [ER membrane]
       │
       ├──► ↓ N-glycosylation (CDG type I)  ──► serum protein hypoglycosylation
       ├──► ↓ O-/C-mannosylation (branch, inferred)
       └──► ↓ GPI-anchor synthesis (branch, inferred)
                    │
                    ▼
      Glycoprotein misfolding / dysfunction (multi-tissue)
                    │
      ┌─────────────┼──────────────┬──────────────┐
      ▼             ▼              ▼              ▼
  Brain/cerebellum  Eye/retina    Skin        Skeleton (progressive)
  ID, hypotonia,    nystagmus,    ichthyosis  kyphosis/scoliosis
  ataxia, hypoplasia optic atrophy,
                    retinal dystrophy,
                    coloboma, cataract
```

Molecular pathway / cellular process / compartment. The defect is in **dolichol biosynthesis** feeding the **protein N-glycosylation (dolichol) cycle** at the **ER membrane**. Key GO terms: GO:0019408 (dolichol biosynthetic process), GO:0006486 (protein glycosylation), GO:0006487 (protein N-linked glycosylation), GO:0006506 (GPI anchor biosynthetic process), GO:0035269 (protein O-linked mannosylation). Cellular compartment: GO:0005789 (endoplasmic reticulum membrane), GO:0005783 (endoplasmic reticulum). Enzyme activity: polyprenol reductase (EC 1.3.1.94).

Metabolic changes. Isoprenoid/dolichol lipid metabolism is directly disrupted (elevated polyprenol, relatively preserved absolute dolichol via the detour pathway). **Immune involvement** is not a primary feature of SRD5A3-CDG (unlike immune-relevant CDG such as MOGS-, PGM3-, VPS13B-CDG). **Molecular profiling** to date is dominated by serum N-

glycoproteomics showing broad hypoglycosylation (PMID: 41732066); a GTEx in-silico study noted that tissue vulnerability in CDG does not simply track baseline gene expression (PMID: 42472049).

Cell types (suggested CL terms): cerebellar Purkinje cell (CL:0000121), photoreceptor cell (CL:0000210), keratinocyte (CL:0000312). **Suggested CHEBI:** polyprenol (CHEBI:26250), dolichol (CHEBI:23514), dolichyl phosphate (Dol-P), dolichyl diphosphate.

7. Anatomical Structures Affected

- **Primary organs/systems:** central nervous system, especially **cerebellum** (UBERON:0002037) and cerebrum; **eye/retina** (UBERON:0000970 / retina UBERON:0000966, optic nerve UBERON:0000941); **skin** (UBERON:0002097).
- **Secondary/progressive involvement: skeleton/spine** (kyphosis, scoliosis; vertebral column UBERON:0002415).
- **Body systems:** nervous, ophthalmic/sensory, integumentary, musculoskeletal.
- **Tissue/cell level:** neural tissue (cerebellar neurons incl. Purkinje cells), retinal photoreceptors, epidermal keratinocytes.
- **Subcellular level: endoplasmic reticulum membrane** (site of the dolichol cycle; GO:0005789) is the primary affected compartment.
- **Lateralization:** manifestations are typically **bilateral/generalized** (e.g., bilateral nystagmus, bilateral optic atrophy, symmetric cerebellar involvement).

8. Temporal Development

- **Onset: Congenital / neonatal-infantile**, with hypotonia, nystagmus, and developmental delay evident early; onset pattern is **chronic/insidious**.
- **Progression:** The cognitive deficit is broadly **static**, while specific features are **progressive** — kyphosis, retinitis pigmentosa, and cataracts develop or worsen over time (PMID: 27480077). Cerebellar structural changes may **appear or become detectable later**, being absent on early MRI in some infants (PMID: 41769439).
- **Course/duration: Chronic, lifelong.** No spontaneous remission. **Critical period:** early childhood neurodevelopment is the key window for supportive/early-intervention therapies; any future disease-modifying therapy would presumably need early initiation.

9. Inheritance and Population

- **Epidemiology:** Ultrarare; **~60 cases reported worldwide**; precise prevalence/incidence are unavailable (well under Orphanet's rare-disease threshold). Dolichol-metabolism disorders were ~5% of the 280-patient FCDGC natural history cohort (PMID: 38959600).
- **Inheritance: Autosomal recessive** (PMID: 20637498).
- **Penetrance:** Complete for biallelic LoF (all reported biallelic carriers are affected), with **variable expressivity** (PMID: 30019980).
- **Anticipation / germline mosaicism:** Not applicable/not reported (non-repeat-expansion disorder).
- **Founder effects / consanguinity:** Documented — p.Gln96delinsX founder allele in Baluchi/South Asian families; frequent consanguinity (PMID: 30019980).
- **Carrier frequency:** Not precisely established; expected very low given rarity.
- **Sex ratio:** ~1:1 (autosomal); no sex predilection. In the FCDGC cohort overall, sexes were roughly balanced (PMID: 38959600).
- **Geographic distribution:** Cases reported across diverse populations (European, South Asian, Middle Eastern, Egyptian, etc.); founder alleles create regional clustering.

10. Diagnostics

Recommended approach. Diagnosis is genetic-first in the modern setting: **exome or genome sequencing** including **intragenic copy-number/structural-variant analysis** (PMID: 35339718), supported by biochemical screening.

Laboratory / biochemical tests: - **Serum transferrin isoelectric focusing / CDT analysis → CDG type I** pattern. Caveat: can be **falsely reassuring** (substantial correctly glycosylated transferrin in some patients) and confounded by transferrin protein variants (PMID: 37876147). - **Polyprenol/dolichol ratio** in fibroblasts (elevated) — biochemical confirmation of the enzyme defect (PMID: 22304929). - **Serum N-glycoproteomics** demonstrating extensive hypoglycosylation (PMID: 41732066); **albumin glycopeptides** as emerging biomarkers (PMID: 41713138).

Imaging / functional / electrophysiology: Brain **MRI** (cerebellar hypoplasia/atrophy — may be normal early); ophthalmologic evaluation with **fundus photography, autofluorescence, and electroretinogram (ERG)** for retinal dystrophy (PMID: 41667393).

Genetic testing modalities: WES and WGS are the highest-yield tools; targeted CDG gene panels including *SRD5A3*; single-gene *SRD5A3* testing (incl. deletion/duplication analysis). Karyotyping, FISH, mitochondrial DNA testing, and repeat-expansion testing are **not applicable**.

Clinical criteria / differential diagnosis. No formal consensus criteria exist; diagnosis rests on the phenotype + CDG-I biochemistry + biallelic *SRD5A3* variants. **Differential diagnosis** includes other CDG type I subtypes (notably **PMM2-CDG**, the most common), other dolichol-pathway CDG (**DHDDS-, DPM1/3-, SRD5A3-**), Leber congenital amaurosis/early-onset retinal dystrophies, and cerebellar hypoplasia syndromes; distinguishing features are the specific combination of retinal dystrophy, coloboma/cataract, ichthyosis, and the elevated polyprenol/dolichol ratio.

Screening. No newborn screening exists for SRD5A3-CDG. Carrier and cascade testing are appropriate in known families.

11. Outcome / Prognosis

- **Survival/mortality:** No formal survival statistics; the disorder is **chronic and compatible with survival into adulthood** (adult patients are described; PMID: 27480077), consistent with residual glycosylation via the alternative dolichol pathway. Severe early presentations (e.g., seizures) can occur (PMID: 41769439).
- **Morbidity/disability:** Substantial and lifelong — intellectual disability, ataxia, and progressive visual loss drive major functional impairment and dependency.
- **Complications/progression:** Progressive kyphosis/scoliosis, retinitis pigmentosa, and cataracts (PMID: 27480077); seizures in a minority.
- **Prognostic factors:** Genotype (null vs hypomorphic), residual enzyme/dolichol pathway activity, and severity of neurodevelopmental involvement are the main determinants; validated prognostic biomarkers are not established. The Nijmegen Progression CDG Rating Scale (NPCRS) is used across CDG to grade severity (PMID: 38959600).

12. Treatment

No disease-modifying therapy is established. Management is **symptomatic and multidisciplinary** (PMID: 41648237; PMID: 39236565): - **Neurodevelopmental:** early intervention, physical/occupational/speech therapy (NCIT: Rehabilitation Therapy). - **Ophthalmologic:** low-vision support, cataract surgery as indicated (NCIT: Cataract Surgery). -

Orthopedic: management of kyphosis/scoliosis. - **Seizure control:** standard antiseizure medications (e.g., levetiracetam is effective in related CDG; PMID: 37955240) (NCIT: Levetiracetam).

Experimental / investigational: - **Atorvastatin repurposing** (HMG-CoA reductase inhibitor) — reported as an experimental strategy in newly developed high-throughput SRD5A3-CDG models (PMID: 41648237). NCIT: Atorvastatin Calcium (C29014). - **Dietary dolichol supplementation** — conceptual, supported by dolichol rescue in plant PPRD2-deficient models (PMID: 26628744). - **Cross-CDG precedents for root-cause "sugar" therapies** (not yet demonstrated for SRD5A3-CDG): D-galactose in PGM1-CDG (PMID: 41182978), oral mannose in MPI-CDG, and epalrestat (aldose reductase inhibitor) in PMM2-CDG (PMID: 34652821) illustrate the emerging targeted-therapy landscape (PMID: 39236565).

Pharmacogenomics, gene/cell/RNA therapy, immunotherapy, surgery-as-cure: No SRD5A3-specific advanced therapeutics exist; these remain future directions.

13. Prevention

- **Primary prevention:** Not applicable at the population level (genetic disease). **Genetic counseling** for at-risk families, carrier testing, and reproductive options (prenatal diagnosis, preimplantation genetic testing) are the principal preventive tools, especially in consanguineous families and founder-allele populations.
- **Secondary prevention:** No population newborn screen; **cascade testing** in known families enables early diagnosis and supportive intervention.
- **Tertiary prevention:** Proactive surveillance and management of progressive complications (vision, spine, seizures) to reduce morbidity.
- **Immunization / public-health / environmental interventions:** Not applicable.

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** The polyprenol→dolichol reduction step is deeply conserved. Human *SRD5A3* has orthologs in *Arabidopsis thaliana* (**PPRD1, PPRD2**; PMID: 26628744) and in **budding yeast** (*Saccharomyces cerevisiae*), where the three-step dolichol "detour" pathway is conserved (PMID: 42201967). Mouse ortholog: *Srd5a3* (PMID: 26346620).
- **Natural/veterinary disease:** No naturally occurring SRD5A3-CDG has been reported in companion animals or wildlife (no OMIA entry identified in this investigation).

- **Comparative biology:** The conservation of the enzyme and the dolichol-rescue phenotype (PPRD2-deficient plants rescued by dolichol) indicates a conserved mechanism linking dolichol supply to protein glycosylation across kingdoms (PMID: 26628744).
- **Transmission / zoonosis:** Not applicable.

15. Model Organisms

Model	Type	Utility / recapitulation	Reference
Arabidopsis thaliana pprd2	Plant genetic	Lethal (male sterility); dolichol shortage; **rescued by dolichol supplementation** — establishes causal role of dolichol/ glycosylation	PMID: 26628744
S. cerevisiae (dolichol detour pathway)	Yeast	Confirms conserved alternative dolichol biosynthesis; tractable for pathway dissection	PMID: 42201967
Patient fibroblasts	In vitro (human)	Elevated polyprenol/dolichol ratio; hypoglycosylation — core biochemical model	PMID: 22304929
High-throughput SRD5A3-CDG disease models	In vitro (recent)	Enabled atorvastatin repurposing screen	PMID: 41648237
Mouse *Srd5a3*	Mammalian	**Gap:** no isolated *Srd5a3*-null disease model characterized; a ~1.2 Mb 5qC3.3 deletion including *Srd5a3* caused peri-implantation lethality attributable to *Exoc1*, not *Srd5a3*	PMID: 26346620

Model limitations. Plant/yeast models capture the enzymatic and glycosylation defect but not the mammalian neuro-ophthalmologic phenotype. The absence of a validated isolated *Srd5a3*-knockout mouse model is a major gap for preclinical therapeutic testing.

Mechanistic Model / Interpretation

SRD5A3-CDG is best understood as a **substrate-supply failure in the dolichol cycle**. The single enzymatic lesion (polyprenol reductase deficiency) sits **upstream** of the entire dolichol-dependent glycosylation machinery. Its immediate, demonstrated consequence is an **elevated polyprenol/dolichol ratio** — polyprenol accumulates because it cannot be reduced, while absolute dolichol is partly preserved by a conserved **alternative/detour biosynthesis pathway**. This residual dolichol is mechanistically important: it explains both the survival of patients (versus embryonic lethality expected from total glycosylation failure) and the observation of substantial correctly glycosylated transferrin in some patients.

Downstream, dolichyl-phosphate limitation throttles assembly of the LLO precursor, producing broad **protein N-hypoglycosylation** (demonstrated by serum glycoproteomics: 245/291 altered glycopeptides decreased). Because dolichol is a shared currency, the defect **branches** to O-/C-mannosylation and GPI-anchor synthesis (inferred). The tissue selectivity of the clinical phenotype — brain/cerebellum, eye/retina, skin — reflects the particular sensitivity of these developing tissues to glycoprotein dysfunction rather than tissue-specific enzyme expression (GTEx analysis found baseline expression does not predict CDG tissue vulnerability). The temporal profile (congenital onset with later-emerging kyphosis, retinitis pigmentosa, cataracts) suggests both a **developmental** component (cerebellar hypoplasia, coloboma) and a slowly **progressive/degenerative** component (retinal, lens, skeletal).

Evidence Base

PMID	Title (abbrev.)	Supports
20637498	*SRD5A3 required for polyprenol→dolichol; mutated in CDG*	F001, F007 — gene function, disease causation, residual pathway
22304929	*Life with too much polyprenol*	F003 — elevated polyprenol/dolichol ratio biomarker
41732066	*Extensive hypoglycosylation of serum N-glycoproteins*	F003 — 245/291 glycopeptides decreased
35339718	*SRD5A3-CDG: intragenic tandem duplication*	F003, F006 — CNV diagnosis; ~23 variants
20700148	*Kahrizi syndrome frameshift in SRD5A3*	F002 — allelic Kahrizi phenotype
31638560	*Review of SRD5A3 variants and ocular findings*	F002 — core clinical features
28253385	*SRD5A3-CDG with early-onset retinal dystrophy*	F002 — retinal dystrophy as presenting feature
27480077	*SRD5A3-CDG adult-onset features*	F006 — progressive kyphosis, RP, cataracts
30019980	*Undiagnosed SRD5A3-CDG girl*	F006 — founder allele, variable expressivity
26628744	*Arabidopsis PPRD2 deficiency*	F005 — orthology, dolichol rescue
42201967	*Dolichol detour pathway conserved in yeast*	F001, F005 — conserved alternative pathway
18077451	*Recycling of dolichyl monophosphate*	F007 — ER dolichol cycle, Dol-P recycling
41648237	*Repurposing atorvastatin for SRD5A3-CDG*	F004 — ~60 cases; experimental therapy
39236565	*Treatment of CDG: an overview*	F004, F008 — symptomatic care; emerging targeted therapies
26346620	*Peri-implantation lethality on 5qC3.3*	F008 — mouse model gap (Exoc1, not Srd5a3)
38959600	*FCDGC natural history cohort (n=280)*	Epidemiology — dolichol disorders ~5%; NPCRS

PMID	Title (abbrev.)	Supports
41769439	*Monozygotic twins, SRD5A3-CDG*	Phenotype diversity; normal early MRI; nonsense variant
41667393	*Egyptian SRD5A3-CDG patient*	Missense p.Tyr170Cys; ERG diagnostics
41713138	*Albumin as a glycoprotein biomarker in CDG*	Emerging albumin glycopeptide biomarker
37876147	*Misleading transferrin variants in CDG*	Diagnostic caveat for transferrin screening
34652821	*Epalrestat/sorbitol in PMM2-CDG*	Cross-CDG targeted-therapy precedent
41182978	*D-galactose in PGM1-CDG*	Cross-CDG dietary-sugar precedent
40902550	*Genetic disorders of dolichol synthesis and utilization*	Review — dolichol pathway/CDG classification

Evidence source types: The evidence base is predominantly **human clinical** (case reports, case series, natural history cohort) and **in vitro** (patient fibroblasts, glycoproteomics), complemented by **model-organism** work in plants and yeast. There are **no** large randomized trials, no validated mammalian in-vivo disease model, and no computational/GWAS studies relevant to this Mendelian disorder.

Limitations and Knowledge Gaps

1. **Small evidence base.** With ~60 cases, all clinical claims derive from case reports/series and one natural history cohort; frequencies are qualitative, and formal prevalence/incidence, survival, and QoL metrics are unavailable.
2. **No validated mammalian disease model.** The absence of a characterized isolated *Srd5a3*-knockout mouse (PMID: 26346620) hampers mechanistic and preclinical therapeutic studies.
3. **Branch mechanisms inferred.** Impairment of O-/C-mannosylation and GPI-anchor synthesis is inferred from shared dolichol dependency rather than directly demonstrated in SRD5A3-CDG patients.

4. **Diagnostic pitfalls.** Transferrin-based screening can be falsely reassuring; intragenic CNVs require dedicated analysis — both risk under-/mis-diagnosis.
5. **No proven therapy.** Atorvastatin repurposing and dolichol supplementation are experimental; no clinical efficacy data exist for SRD5A3-CDG.
6. **Genotype–phenotype correlation is weak.** Variable expressivity (even for identical alleles) is unexplained; modifier genes and the quantitative contribution of the alternative dolichol pathway are undefined.

Proposed Follow-up Experiments / Actions

1. **Generate a conditional/tissue-specific *Srd5a3* mouse model** (e.g., neural- and eye-restricted knockouts) to overcome the peri-implantation lethality confounded by *Exoc1*, enabling phenotype recapitulation and therapeutic testing.
2. **Validate atorvastatin efficacy** in patient-derived models (iPSC-derived neurons/organoids, cerebellar and retinal organoids) and, if positive, design an n-of-few clinical trial with glycosylation biomarkers as endpoints (PMID: 41648237).
3. **Test dietary dolichol supplementation** rescue in mammalian patient-derived systems, building on plant/yeast rescue data (PMID: 26628744).
4. **Directly quantify O-/C-mannosylation and GPI-anchor defects** in patient cells to confirm the inferred mechanistic branches.
5. **Standardize diagnostics:** adopt reflex confirmatory testing (polyprenol/dolichol ratio, glycoproteomics, CNV analysis) whenever transferrin screening is normal but clinical suspicion is high; evaluate **albumin glycopeptides** as a robust biomarker (PMID: 41713138).
6. **Enroll SRD5A3-CDG patients in the FCDGC natural history study** to build prospective longitudinal outcome, NPCRS severity, and QoL data (PMID: 38959600).
7. **Map founder alleles and carrier frequencies** in high-consanguinity populations to guide carrier screening and reproductive counseling.

Report compiled from 8 confirmed findings across 35 reviewed publications. Evidence is predominantly human-clinical and in-vitro, supplemented by conserved plant/yeast models. All mechanistic and clinical claims are cited to primary literature by PMID; inferred steps are explicitly labeled.
