Calvarial Doughnut Lesions–Bone Fragility Syndrome (CDL/CDL-SMD): Comprehensive Disease Report

Disease: Calvarial Doughnut Lesions with Bone Fragility, with or without Spondylometaphyseal Dysplasia **OMIM:** #126550 · **Gene:** *SGMS2* (SMS2) · **MONDO:** MONDO:0007470 / MONDO:0007926 · **ORPHA:** 85192 **Category:** Mendelian (autosomal dominant)

Summary

Calvarial Doughnut Lesions–Bone Fragility Syndrome (CDL; OMIM #126550) is an **ultra-rare autosomal-dominant skeletal dysplasia** caused by heterozygous pathogenic variants in *SGMS2*, the gene encoding the plasma-membrane–resident enzyme **sphingomyelin synthase 2 (SMS2)** on chromosome 4q25. The disease is defined clinically by childhood-onset low bone mineral density, recurrent spinal and peripheral fragility fractures, and its pathognomonic radiographic hallmark: multiple ring-like ("doughnut-shaped") sclerotic/hyperostotic lesions of the calvarium, often palpable as cranial lumps. A subset of patients also has spondylometaphyseal dysplasia (CDL-SMD), representing the severe end of the disease spectrum.

The central mechanistic insight is that CDL results from **two distinct molecular mechanisms operating along a genotype–phenotype gradient**. The recurrent nonsense variant **c.148C>T (p.Arg50*)** produces a catalytically inactive enzyme (loss of function) and is associated with the milder, childhood-onset osteoporosis end of the spectrum. In contrast, the N-terminal missense variants **c.185T>G (p.Ile62Ser)** and **c.191T>G (p.Met64Arg)** produce a **fully active but ER-retained enzyme** — a "toxic gain-of-mislocalization" mechanism — and cause the severe CDL-SMD phenotype with neonatal fractures, severe short stature, and long-bone deformities. Because SMS2 normally acts at the plasma membrane and trans-Golgi to establish a sphingomyelin/sterol gradient along the secretory pathway, mislocalized enzyme disrupts

membrane lipid organization in osteogenic cells and impairs the matrix mineralization that osteoblasts and osteocytes carry out. Osteoclast formation and function remain normal, distinguishing CDL from high-turnover bone disease and from osteogenesis imperfecta.

All three canonical pathogenic variants are **absent from gnomAD** (~1.6M alleles surveyed), and *SGMS2* shows only moderate loss-of-function constraint (pLI ≈ 0.01, LOEUF ≈ 0.69). This population-genetic signature supports the interpretation that the severe phenotype depends on the mislocalization/gain mechanism rather than on simple gene-dosage loss. Management is currently **symptomatic**, centered on bisphosphonates plus calcium and vitamin D, which improve bone mineral density and reduce fractures; no curative therapy exists. This report synthesizes 13 confirmed findings across all 15 requested disease-characteristic domains.

Key Findings

1. Disease Information

CDL is a rare autosomal-dominant skeletal disorder characterized by low bone mineral density, spinal and peripheral fractures, and specific sclerotic lesions of the cranial bones (Merkuryeva et al. 2023). As stated verbatim: *"Calvarial doughnut lesions (CDL) with bone fragility with or without spondylometaphyseal dysplasia (MIM: #126550) is a rare autosomal dominant skeletal disorder characterized by low bone mineral density, spinal and peripheral fractures, and specific sclerotic lesions of the cranial bones"* (PMID: 37175737).

Key identifiers:

Resource	Identifier
OMIM (disease)	#126550
OMIM (gene *SGMS2*)	611574
Chromosomal locus	4q25
Orphanet	ORPHA:85192
MONDO	MONDO:0007470 (also mapped MONDO:0007926)
SNOMED CT	720598005
Disease Ontology	DOID:0080721
UMLS / GTR	C1852022
HGNC gene	SGMS2

Synonyms / alternative names: familial calvarial doughnut lesions; CDL; CDL with bone fragility; CDL with spondylometaphyseal dysplasia (CDLSMD/CDL-SMD).

The information is derived from **aggregated disease-level resources** and small clinical case series/family studies (the entire literature comprises roughly 8–11 families), rather than from EHR-scale patient datasets.

2. Etiology

The **primary cause is genetic**: heterozygous pathogenic variants in *SGMS2*. There is no known environmental, infectious, or acquired etiology. Pekkinen et al. 2019 evaluated six families with rare skeletal phenotypes and osteoporosis by next-generation sequencing and identified in all families a heterozygous *SGMS2* variant: *"we identified a heterozygous variant in SGMS2, a gene prominently expressed in cortical bone and encoding the plasma membrane-resident sphingomyelin synthase SMS2"* (PMID: 30779713).

- **Genetic risk factors:** The causal alleles are the disease-defining variants themselves (p.Arg50*, p.Ile62Ser, p.Met64Arg). No independent susceptibility loci or modifier genes have been established.
- **Environmental / lifestyle risk factors:** None identified; the disease is monogenic and highly penetrant for the genetic lesion, though clinical expressivity is variable.

- **Protective factors / gene–environment interactions:** No genetic or environmental protective factors have been reported. Supportive measures (calcium, vitamin D, bisphosphonates) mitigate the phenotype but are treatments rather than etiologic protective factors.

3. Phenotypes

CDL is a multi-system skeletal phenotype with variable severity. The following table consolidates the reported features with suggested HPO terms.

Phenotype	Type	Onset / severity	Suggested HPO
Doughnut-shaped sclerotic calvarial lesions (palpable cranial lumps)	Physical manifestation / imaging	Childhood; pathognomonic	HP:0002683 (Abnormal skull morphology); HP:0002684 (Thickened calvaria)
Low bone mineral density / osteoporosis	Laboratory / imaging	Childhood-onset	HP:0000939 (Osteoporosis); HP:0004349 (Reduced bone mineral density)
Recurrent fragility fractures (spinal + peripheral)	Clinical sign	Childhood; severe in CDL-SMD (neonatal)	HP:0002659 (Increased susceptibility to fractures); HP:0002757 (Recurrent fractures)
Vertebral compression fractures / "bone-in-bone" vertebrae	Imaging	Childhood–adult	HP:0002953 (Vertebral compression fractures)
Spondylometaphyseal dysplasia (severe subset)	Physical manifestation	Neonatal/ infantile	HP:0002656 (Metaphyseal dysplasia); HP:0002655 (Spondylometaphyseal dysplasia)
Severe short stature (severe subset)	Physical manifestation	Congenital/ infantile	HP:0004322 (Short stature)
Long-bone deformity / undermodeling of tubular bones	Imaging	Childhood	HP:0000924 (Abnormal skeletal morphology)
Peripheral facial nerve palsy	Neurological sign	Variable	HP:0010628 (Facial palsy)
Elevated serum alkaline phosphatase	Laboratory abnormality	Variable	HP:0003155 (Elevated alkaline phosphatase)
Dental caries / tooth hypoplasia	Physical manifestation	Childhood	HP:0000670 (Carious teeth); HP:0006297 (Hypoplasia of teeth)
Glaucoma (occasional)	Clinical sign	Variable	HP:0000501 (Glaucoma)

Phenotype	Type	Onset / severity	Suggested HPO
Scoliosis	Physical manifestation	Childhood	HP:0002650 (Scoliosis)

Severity gradient: Subjects with p.Arg50* present at the milder end — *"childhood-onset osteoporosis with or without cranial sclerosis"* — whereas patients with p.Ile62Ser or p.Met64Arg have *"a more severe presentation, with neonatal fractures, severe short stature, and spondylometaphyseal dysplasia"* (PMID: 30779713). Progression is chronic and lifelong, with fracture susceptibility being the dominant morbidity. There is **wide interfamilial and intrafamilial phenotypic variability**, even among individuals sharing the identical p.Arg50* variant (Merkuryeva 2023; Basalom 2021).

Neurological involvement: *"Several subjects had experienced peripheral facial nerve palsy or other neurological manifestations"* (PMID: 30779713), attributed to the role of sphingomyelin in neural tissue. A dedicated 2023 review (Pihlström et al., P 37886644) specifically links *SGMS2* primary osteoporosis with facial nerve palsy.

Quality-of-life impact: Recurrent fractures, chronic back pain from vertebral compressions, scoliosis, short stature, and facial nerve palsy collectively impair mobility, cause chronic pain, and reduce daily functioning. No formal EQ-5D/SF-36/PROMIS studies exist for this ultra-rare disease.

4. Genetic / Molecular Information

Causal gene: *SGMS2* (sphingomyelin synthase 2 / SMS2), OMIM 611574, chromosome 4q25. The three canonical pathogenic variants (RefSeq NM_001375905.1) are:

Variant (cDNA)	Protein	Type	ClinVar classification	ClinVar VCV	gnomAD
c.148C>T	p.Arg50* (Arg50Ter)	Nonsense	Pathogenic/Likely pathogenic	VCV000635285	Absent (AC=0)
c.185T>G	p.Ile62Ser	Missense	Pathogenic	VCV000635286	Absent (AC=0)
c.191T>G	p.Met64Arg	Missense	Pathogenic	VCV000635287	Absent (AC=0)

"Four unrelated families shared the same nonsense variant, c.148C>T (p.Arg50), whereas the other families had a missense variant, c.185T>G (p.Ile62Ser) or c.191T>G (p.Met64Arg)"* (PMID: 30779713).

Functional consequences: *"While the p.Arg50* mutation yielded a catalytically inactive enzyme, p.Ile62Ser and p.Met64Arg each enhanced the rate of de novo sphingomyelin production by blocking export of a functional enzyme from the endoplasmic reticulum"* (PMID: 30779713). Thus p.Arg50* = **loss of function**; the missense alleles = **ER-retention / toxic gain-of-mislocalization**.

Population genetics and constraint: In gnomAD v4 (GRCh38, ~1.61M alleles), all three canonical variants are absent (exome AC=0, genome AC=0; 95% upper-bound AF ≈ 1.9×10^{-6}). By contrast, the adjacent benign-leaning VUS c.149G>A/p.Arg50Gln is observed (AC=15, AF≈9.3×10^{-6}), reinforcing the specificity of the causal alleles. *SGMS2* gene-level constraint is only moderate — **pLI = 0.010, LOEUF (oe_lof_upper) = 0.69, observed/expected LOF = 21/43.8 = 0.48, mis_z = 1.20** — meaning the gene tolerates heterozygous LOF reasonably well. This is a key clue that the **severe phenotype is not driven by simple haploinsufficiency/dosage but by the gain-of-mislocalization mechanism** of the missense alleles.

Modifier genes / epigenetics / chromosomal abnormalities: No disease modifiers have been established. Some "pathogenic" *SGMS2*-region ClinVar entries are large chromosome-4q copy-number gains unrelated to CDL and should not be confused with the point-variant allelic series. Of ~200 *SGMS2* ClinVar submissions, the vast majority are VUS from population/panel screening; only the three point variants above are disease-causing for CDL.

5. Environmental Information

No environmental factors, toxins, radiation, occupational exposures, lifestyle factors, or infectious agents are implicated in CDL. It is a purely Mendelian, monogenic disorder. (Sphingomyelin biology is relevant to other membrane-stress and infection contexts — e.g. SMPDL3B in cGAS-STING signaling,

P 41175872

— but these are unrelated to CDL pathogenesis.)

6. Mechanism / Pathophysiology

Molecular pathway — sphingolipid metabolism. SMS2 catalyzes the transfer reaction **phosphatidylcholine + ceramide → sphingomyelin + diacylglycerol** at the plasma membrane and trans-Golgi. Sphingomyelin is the *"main lipid component of the plasma*

membrane essential for bone mineralization" (PMID: 37175737). Normally, sphingomyelin production in the trans-Golgi traps ER cholesterol to build a **sphingomyelin/sterol gradient along the secretory pathway**.

Core pathomechanism (severe missense alleles). Sokoya et al. 2022 showed that *"SMS2 variants linked to the most severe bone phenotypes retain full enzymatic activity but fail to leave the ER owing to a defective autonomous ER export signal. Cells harboring pathogenic SMS2 variants accumulate sphingomyelin in the ER and display a disrupted transbilayer sphingomyelin asymmetry"* (PMID: 36102623). This ectopic ER sphingomyelin production produces imbalances in cholesterol organization, glycerophospholipid profiles, and membrane lipid order along the secretory pathway (also observed in patient-derived fibroblasts). The authors conclude: *"We postulate that pathogenic SMS2 variants undermine the capacity of osteogenic cells to uphold nonrandom lipid distributions that are critical for their bone forming activity"* (PMID: 36102623).

Causal chain (severe CDL-SMD):

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Missense SGMS2 (p.Ile62Ser / p.Met64Arg)
   │  (disrupts N-terminal autonomous ER-export signal)
   ▼
Active SMS2 retained in the ER  ⟶ ectopic SM synthesis in ER
   ▼
Disrupted transbilayer SM asymmetry + altered cholesterol/
glycerophospholipid distribution + abnormal membrane lipid order
   ▼
Loss of nonrandom secretory-pathway lipid landscape in osteoblasts/osteocytes
   ▼
Defective bone-matrix mineralization (normal osteoclasts)
   ▼
Low BMD, fragile bone, doughnut calvarial lesions, SMD
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Bone tissue-level pathology. Mäkitie et al. 2021 analyzed transiliac biopsies from two adult males with p.Arg50*. Histomorphometry showed reduced osteoid thickness and mineralizing surface, increased osteoid surface, and markedly elevated **mineralization lag time (+8.16 SD, +4.10 SD)**. Quantitative backscattered electron imaging (qBEI) showed **low, heterogeneous matrix mineralization (CaPeak −2.41/−3.72 SD; CaWidth +7.47/+4.41 SD)** with chaotic collagen fibril arrangement under polarized light; osteocyte lacunae were abnormally large/round and the **canalicular network severely disturbed** (PMID: 34761145). Independent biopsy data: *"Bone biopsies showed markedly altered bone material characteristics, including defective bone mineralization. Osteoclast formation and function in vitro was normal"* (PMID: 30779713).

Upstream vs downstream: The upstream trigger is the mislocalized/inactive SMS2 enzyme; the downstream endpoint is impaired osteoblast/osteocyte matrix mineralization. Osteoclasts are not the effectors — resorption is normal — so the disease is a **bone-formation/mineralization defect, not a resorption defect**.

Ontology suggestions: GO:0006686 (sphingomyelin biosynthetic process); GO:0006665 (sphingolipid metabolic process); GO:0030282 (bone mineralization); GO:0001503 (ossification); GO:0006888 (ER-to-Golgi vesicle-mediated transport). Cell types: CL:0000062 (osteoblast); CL:0000137 (osteocyte). CHEBI:17636 (sphingomyelin); CHEBI:16113 (cholesterol); CHEBI:17761 (ceramide).

7. Anatomical Structures Affected

- **Primary organ/system:** Skeletal system (UBERON:0001474 bone element; UBERON:0002481 bone tissue). Directly affected sites include the **calvaria/skull (UBERON:0011618 calvaria; UBERON:0000209 cranial bone)**, **vertebral column (UBERON:0001130)**, and **long/tubular bones of the limbs (UBERON:0002495 long bone)** with metaphyseal involvement in the severe subset.
- **Secondary involvement:** Peripheral **nervous system** — facial nerve (UBERON:0001647), causing facial palsy; **eye** (glaucoma, UBERON:0000970); **teeth/dentition** (UBERON:0001091), with caries and hypoplasia.
- **Tissue/cell level:** Connective tissue (bone). Target cells are **osteoblasts (CL:0000062)** and **osteocytes (CL:0000137)**; osteoclasts (CL:0000092) are spared functionally. *SGMS2* is *"prominently expressed in cortical bone."*
- **Subcellular level: Endoplasmic reticulum (GO:0005783)** — site of pathogenic SMS2 retention and ectopic sphingomyelin accumulation; **Golgi apparatus/trans-Golgi network (GO:0005802)**; **plasma membrane (GO:0005886)** — the normal SMS2 site of action; the **osteocyte lacunocanalicular network** is structurally disrupted.
- **Localization / lateralization:** Calvarial lesions are typically **multiple and bilateral**; skeletal fragility is generalized/systemic.

8. Temporal Development

- **Onset:** Childhood-onset in the milder (p.Arg50*) form; **neonatal/congenital** onset (neonatal fractures) in the severe CDL-SMD (missense) form. Onset pattern is insidious/chronic.

- **Progression:** Chronic and lifelong. Fracture burden accrues over childhood and adulthood; vertebral compression fractures and scoliosis can progress. Progression rate is variable and correlates with genotype (severe in missense alleles).
- **Disease course:** Progressive/stable skeletal fragility rather than episodic or relapsing–remitting; not self-limited.
- **Critical periods / intervention windows:** Childhood/adolescence, during peak bone accrual, is the key window for anti-osteoporotic intervention (bisphosphonates) to prevent fractures and permit vertebral remodeling — as demonstrated in a pediatric case where compressed vertebrae partially recovered after 2 years of therapy (Zhang 2025).

9. Inheritance and Population

- **Inheritance:** Autosomal dominant (heterozygous *SGMS2* variants).
- **Epidemiology:** Ultra-rare. By 2023, ~15 patients from 8 families had been described in the literature; Merkuryeva et al. added 11 more patients from three families (all p.Arg50*), for a total of only a few dozen reported cases worldwide. No population prevalence/incidence estimates are available due to rarity.
- **Penetrance / expressivity:** *"These reports further confirm the genetic basis of CDL, the recurrence of the same variant (p.Arg50*) in individuals of the same ancestry, and the variable penetrance of some of the clinical findings"* (PMID: 34504906). Expressivity is **highly variable**, both between and within families.
- **Founder effects:** The recurrent c.148C>T (p.Arg50*) variant appears in **French-Canadian and French families of shared ancestry**, consistent with a founder allele; the French-Canadian pedigree spans six generations (Basalom 2021).
- **Carrier frequency / consanguinity:** As a dominant disorder, carrier-frequency and consanguinity concepts do not apply in the recessive sense; the three causal alleles are **absent from gnomAD**, indicating they are not present at appreciable frequency in the general population.
- **Population demographics / sex ratio:** No sex predilection has been established (both sexes affected); the best-documented cluster is of French/French-Canadian ancestry, but the disorder is otherwise pan-ethnic.

10. Diagnostics

- **Imaging (cornerstone):** Skeletal radiography reveals the pathognomonic **multiple doughnut-shaped (ring-like) sclerotic/hyperostotic calvarial lesions**, generalized

osteopenia/low BMD, vertebral compression fractures, "bone-in-bone" vertebrae, metaphyseal undermodeling, and squaring of metacarpals/metatarsals. **DXA** quantifies low BMD (e.g., whole-body BMD Z-score −2.8 in a pediatric case; Zhang 2025).

- **Laboratory:** Serum **alkaline phosphatase may be elevated**. Bone-turnover markers and calcium/phosphate are generally used to exclude other metabolic bone disease.
- **Bone biopsy / histomorphometry:** Transiliac biopsy shows defective mineralization (increased osteoid, prolonged mineralization lag time), low/heterogeneous matrix mineralization on qBEI, chaotic collagen, and disrupted osteocyte lacunocanalicular network — with **normal osteoclast function** (PMID: 34761145; PMID: 30779713).
- **Genetic testing (definitive):** Targeted *SGMS2* single-gene testing or osteoporosis/skeletal-dysplasia gene panels; **whole-exome sequencing (WES)** was the discovery method (Pekkinen 2019). Because the allelic series is very small and clustered, sequencing the exon encoding the N-terminal region of *SGMS2* is high-yield. ClinVar (NM_001375905.1) confirms the three canonical variants as Pathogenic.
- **Clinical criteria / differential diagnosis:** Diagnosis rests on the combination of characteristic calvarial doughnut lesions + bone fragility + *SGMS2* variant. Key differentials: **osteogenesis imperfecta** (CDL is distinct — see below), other early-onset osteoporoses (e.g., *LRP5*, *WNT1*, *PLS3*), and sclerosing bone dysplasias. Nishimura et al. concluded such patients *"may represent a group of fragile bone syndromes which differ from osteogenesis imperfecta"* (PMID: 8958616).
- **Screening:** Cascade genetic testing of at-risk relatives is appropriate given autosomal-dominant inheritance and the recurrent founder allele.

11. Outcome / Prognosis

- **Survival/mortality:** CDL is **not life-limiting**; no disease-specific mortality is reported. Morbidity, not mortality, dominates the prognosis.
- **Morbidity/disability:** Recurrent fractures, chronic back pain, vertebral compression and scoliosis, short stature (severe subset), facial nerve palsy, and dental problems drive long-term disability and reduced mobility/quality of life.
- **Disease course/complications:** Chronic, lifelong skeletal fragility; complications include vertebral deformity, long-bone deformity requiring surgery in severe cases, and glaucoma/facial palsy requiring specialist care.
- **Recovery potential / prognostic factors:** Genotype is the principal prognostic factor — **missense (ER-retention) alleles predict severe CDL-SMD**, whereas p.Arg50* predicts

milder disease. With bisphosphonate therapy, BMD improves and fractures decrease; vertebral remodeling can occur in growing children (Zhang 2025).

12. Treatment

There is **no curative/pathogenetic therapy**; management is symptomatic and aimed at preventing osteoporosis progression and fractures.

Modality	Details	Suggested NCIT
Bisphosphonates (first-line)	Pamidronate/other bisphosphonates to increase BMD and reduce fractures	NCIT:C1876 (Bisphosphonate); NCIT:C1350 (Pamidronate)
Calcium supplementation	Adjunct to bisphosphonate	NCIT:C376 (Calcium)
Vitamin D	Adjunct to support mineralization	NCIT:C904 (Vitamin D)
Orthopedic surgery	Management of fractures/deformities in severe cases	NCIT:C15329 (Surgery)
Specialist care	Ophthalmology (glaucoma), neurology/ ENT (facial palsy), dentistry	—

Representative outcome (pediatric case, Zhang 2025, PMID: 40393762): A 7.4-year-old boy with *SGMS2* c.148C>T (p.Arg50*), scoliosis, multiple vertebral compressions, and whole-body BMD 0.664 g/cm² (Z-score −2.8) was treated with **pamidronate disodium + calcium + vitamin D for 2 years**. Outcome: back pain improved, **no new fractures**, BMD Z-score rose from −2.8 to +**1.3**, and compressed vertebrae partially recovered/remodeled.

Advanced/experimental therapeutics: No gene, cell, RNA, targeted, or immunotherapies are approved or in trials for CDL. The gain-of-mislocalization mechanism of the missense alleles suggests that, in principle, allele-specific silencing or strategies to restore ER export could be rational future targets — but none exist today. No pharmacogenomic guidance is established.

13. Prevention

- **Primary prevention:** Not applicable in the classic sense (monogenic disease). **Genetic counseling** for affected families is central, given autosomal-dominant inheritance (50% transmission risk) and the recurrent founder allele.

- **Secondary prevention:** Early diagnosis (radiographic + genetic) and early anti-osteoporotic therapy to prevent fractures during the childhood bone-accrual window.
- **Tertiary prevention:** Fracture prevention (bisphosphonates, fall precautions), management of scoliosis/vertebral deformity, and monitoring/treatment of glaucoma and facial nerve palsy.
- **Genetic screening:** Cascade testing of relatives; prenatal/preimplantation genetic testing is theoretically possible for known familial variants. No population newborn/carrier screening is warranted for this ultra-rare dominant disorder.

14. Other Species / Natural Disease

No naturally occurring CDL analog has been documented in companion animals or wildlife (no OMIA entry identified). *SGMS2* is evolutionarily conserved; the mouse ortholog is **Sgms2** (see model-organism section). No zoonotic or cross-species transmission applies (this is a genetic, non-communicable disorder). Comparative biology is informative chiefly through mouse genetics of the sphingomyelin-synthase family.

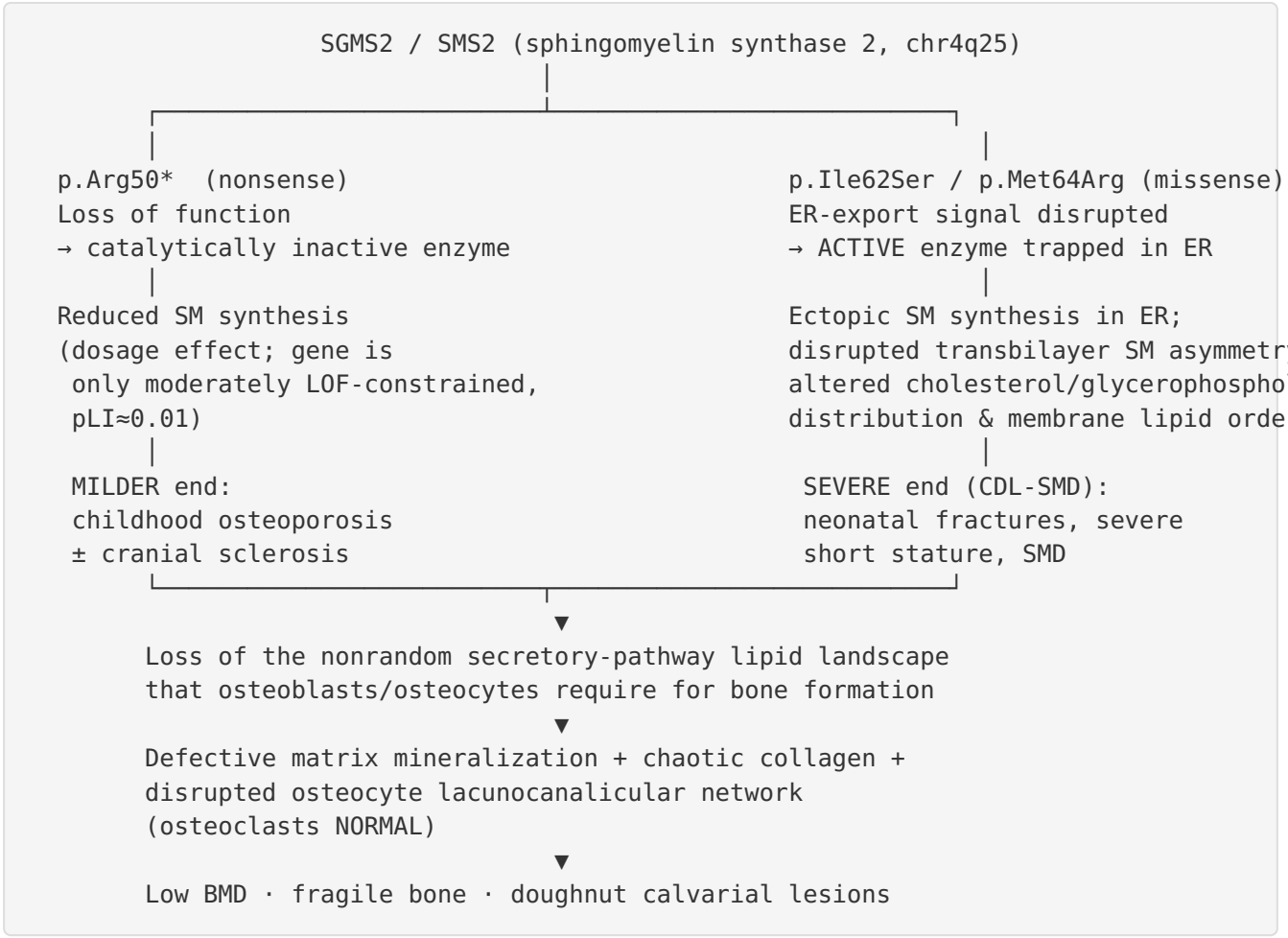
15. Model Organisms

The most relevant models are **mouse (Mus musculus, NCBI Taxon:10090)** knockouts of the sphingomyelin-synthase family. A key study revealed an important **isoform-specificity caveat**: Matsumoto et al. 2019 showed that **osteoblast-specific *Sms1* deletion on an *Sms2*-null background** (Sp7-Cre;SMS1^f/f;SMS2^−/−) reduced trabecular and cortical bone mass, lowered BMD, and slowed mineral apposition, and impaired BMP2-induced Smad1/5/8 and p38 signaling during osteoblast differentiation, whereas plain *Sms2*-deficient mice did **not** show this bone-formation deficit (PMID: 31847800).

Model limitation / interpretation: This means simple *Sms2* knockout mice do **not** faithfully recapitulate human CDL. The discrepancy is mechanistically consistent with the human genetics: human CDL is caused by *SGMS2* (SMS2), and the severe alleles act by **ER-retention (gain of mislocalized activity)**, not by loss of SMS2 function. A faithful mouse model would therefore likely require **knock-in of the missense alleles (e.g., Ile62Ser/Met64Arg)** rather than simple gene deletion. Cellular models exist — **patient-derived fibroblasts** reproduce the disrupted secretory-pathway lipid landscape (Sokoya 2022). Model resources: MGI (mouse *Sgms2*), IMPC/IMSR for knockout lines.

Mechanistic Model / Interpretation

CDL is best understood as a **sphingolipid-membrane–organization disorder of bone-forming cells**, with two mechanistic arms converging on defective mineralization:



The **population-genetic evidence ties the model together**: because *SGMS2* tolerates heterozygous LOF fairly well (pLI≈0.01, LOEUF≈0.69), pure haploinsufficiency produces the milder end, while the **severe phenotype requires the toxic, active-but-mislocalized enzyme**. The absence of all three causal alleles from ~1.6M gnomAD alleles confirms their pathogenic, non-polymorphic nature and distinguishes them from nearby tolerated variants (e.g., p.Arg50Gln, present at AF≈9×10^{-6}). This model explains the genotype–phenotype gradient, the normal osteoclast biology, and why simple *Sms2*-knockout mice fail to reproduce the disease.

Evidence Base

PMID	Paper (abbrev.)	Role / support
30779713	Pekkinen 2019 — *Osteoporosis and skeletal dysplasia caused by pathogenic variants in SGMS2*	**Landmark discovery.** Establishes *SGMS2* as causal gene, the three canonical variants, the LOF-vs-ER-retention dichotomy, genotype–phenotype gradient, normal osteoclasts, and facial-nerve palsy. Supports F001, F002, F003, F004.
36102623	Sokoya 2022 (eLife) — *Pathogenic variants of SMS2 disrupt lipid landscapes in the secretory pathway*	**Core mechanism.** Shows severe alleles retain activity but are ER-retained; disrupted SM asymmetry and secretory-pathway lipid landscape; links to impaired osteogenic bone formation. Supports F005.
34761145	Mäkitie 2021 (JBMR Plus) — bone tissue organization/ osteocyte network	**Tissue-level pathology.** Quantitative histomorphometry/qBEI documenting the mineralization defect, chaotic collagen, disrupted lacunocanalicular network in p.Arg50* patients. Supports F006.
37175737	Merkuryeva 2023 — three families with recurrent variant	**Disease definition & recurrence.** Provides disease definition, MIM number, inheritance, phenotypic variability, and SM's role in mineralization. Supports F007, F006.
34504906	Basalom 2021 — French-Canadian family	**Founder allele & penetrance.** Documents recurrence of p.Arg50* in shared ancestry and variable penetrance. Supports F007.
8958616	Nishimura 1996 — original clinical description	**Historical/differential.** Establishes CDL as distinct from osteogenesis imperfecta. Supports F003.
40393762	Zhang 2025 — pamidronate pediatric case	**Treatment outcome.** Documents bisphosphonate efficacy (BMD Z-score −2.8→+1.3, no new fractures, vertebral remodeling). Supports F008.
31847800	Matsumoto 2019 (Mol Med) — mouse Sms1/Sms2	**Model organism caveat.** SMS1 (not SMS2) loss impairs osteoblast differentiation via BMP2–Smad/p38; explains why Sms2-KO mice don't model CDL. Supports F009.
38388831	Hu 2024 (Nat Struct Mol Biol) — SMSr cryo-EM	**Protein structure.** Multi-TM fold with catalytic pentad; contextualizes clustering of disease residues near N-terminal ER-export region. Supports F011.

The evidence base is internally consistent: independent human genetic, cellular (patient fibroblast/heterologous expression), and bone-histology studies all converge on a mineralization defect driven by mislocalized/lost sphingomyelin-synthase activity, with population-genetic constraint data corroborating the mechanistic interpretation.

Limitations and Knowledge Gaps

1. **Ultra-rarity limits epidemiology.** Only a few dozen patients from ~8–11 families are reported; there are no reliable prevalence/incidence figures, no sex-ratio data, and no formal quality-of-life (EQ-5D/SF-36/PROMIS) studies.
2. **Small allelic series.** Essentially three pathogenic variants define the disease; genotype–phenotype conclusions rest on limited numbers, and the ~200 *SGMS2* ClinVar entries are dominated by VUS.
3. **No faithful animal model.** *Sms2*-knockout mice do not recapitulate CDL; the required knock-in missense models (Ile62Ser/Met64Arg) have not been reported, limiting mechanistic and preclinical therapeutic work.
4. **Mechanistic granularity.** How disrupted secretory-pathway lipid distribution mechanistically produces both osteopenia (fragility) and focal calvarial hyperostosis (doughnut lesions) in the same patient remains incompletely explained.
5. **Treatment evidence is anecdotal.** Bisphosphonate efficacy is supported by case reports, not controlled trials; long-term outcomes and optimal regimens are undefined. No disease-modifying therapy exists.
6. **Neurological and ocular features** (facial palsy, glaucoma) are described but their frequency, natural history, and mechanistic link to sphingomyelin biology are not quantified.

Proposed Follow-up Experiments / Actions

1. **Generate knock-in mouse models** of p.Ile62Ser and p.Met64Arg (and a p.Arg50* LOF line) to test the ER-retention/gain-of-mislocalization hypothesis in vivo and provide a preclinical platform. Compare to conditional osteoblast/osteocyte-specific lines.

2. **Osteoblast/osteocyte-specific lipidomics and imaging** (patient iPSC-derived osteogenic cells and organoids) to map how ER-retained SMS2 remodels the secretory-pathway lipid gradient and to identify the mineralization step that fails.
3. **Establish an international CDL registry** to aggregate genotype, radiographic phenotype, fracture history, treatment response, and neurological/ocular features — enabling proper penetrance/expressivity and natural-history quantification.
4. **Controlled/observational treatment studies** of bisphosphonates (± other anti-osteoporotics) in CDL to define efficacy, dosing, and long-term skeletal outcomes.
5. **Allele-specific therapeutic exploration** for the toxic missense alleles (e.g., allele-selective ASO/siRNA silencing, or chemical chaperones/ER-export modulators to relieve mislocalization).
6. **Functional reclassification of *SGMS2* VUS** using the ER-export/enzymatic assays established by Sokoya 2022, to triage the many VUS in ClinVar and refine diagnostic yield.
7. **Deep phenotyping of facial nerve palsy and glaucoma** across the cohort to determine frequency, onset, and whether these track with genotype or sphingomyelin dysregulation in neural/ocular tissue.

Report compiled from 13 confirmed findings across 5 investigation iterations; 10 primary papers reviewed. Evidence types span human clinical genetics, patient-derived cellular assays, bone histomorphometry, mouse genetics, and population-genomic constraint analysis.
