

Camptodactyly–Arthropathy–Coxa Vara–Pericarditis (CACP) Syndrome: A Comprehensive Disease Characteristics Report

Disease: Camptodactyly–Arthropathy–Coxa Vara–Pericarditis Syndrome **MONDO ID:** MONDO:0008828 · **OMIM:** 208250 · **Causal gene:** *PRG4* (lubricin / proteoglycan 4) **Category:** Mendelian (autosomal recessive)

Summary

Camptodactyly–Arthropathy–Coxa Vara–Pericarditis (CACP) syndrome is an ultra-rare, autosomal recessive Mendelian disorder caused by **biallelic loss-of-function mutations in *PRG4***, the gene encoding **lubricin** (also known as proteoglycan 4, superficial zone protein, or megakaryocyte-stimulating factor precursor). Lubricin is a large secreted, mucin-like glycoprotein that provides **boundary lubrication** to articular cartilage and serosal (pericardial, pleural, tendon-sheath) surfaces and simultaneously **suppresses the overgrowth of synovial intimal cells**. When lubricin is absent, two coupled pathological processes occur: friction-driven death of superficial-zone chondrocytes and uncontrolled synovial intimal hyperplasia. Together these drive the disease's characteristic non-inflammatory tetrad: congenital **camptodactyly** (flexion contractures of the fingers), early-childhood **non-inflammatory large-joint arthropathy** with synovial hyperplasia, progressive **coxa vara** with a short femoral neck, and non-inflammatory serosal (**pericardial/pleural**) effusions.

A central clinical theme — recurring across essentially every modern case series — is that CACP is **repeatedly misdiagnosed as juvenile idiopathic arthritis (JIA)** and treated, ineffectively, with NSAIDs, methotrexate, corticosteroids, and biologic TNF inhibitors. The key distinguishing features are **persistently normal inflammatory markers (ESR/CRP), non-inflammatory synovial fluid (low white-cell count), absence of erosions on imaging, and the presence of coxa vara/short femoral neck**. Definitive diagnosis is made by *PRG4*

sequencing (whole-exome/whole-genome or single-gene), which typically reveals homozygous (or compound heterozygous) **truncating** variants in consanguineous families, supported by an antibody-based assay showing **lubricin absence in blood and synovial fluid**.

There is **no approved disease-modifying treatment**; management is supportive (physiotherapy, orthopedic correction of coxa vara, joint replacement for end-stage disease, pericardiectomy for constrictive pericarditis). The most mechanistically rational investigational therapy is **recombinant human PRG4 (rhPRG4) replacement**, supported by preclinical large-animal and in vitro data. Prognosis is dominated by progressive joint deformity/disability, with **cardiac serositis (constrictive pericarditis) representing the principal life-threatening complication**; cognition and lifespan are otherwise generally preserved.

Key Findings

Finding 1 — CACP is caused by biallelic loss-of-function mutations in *PRG4* (lubricin)

CACP was mapped and cloned by positional-candidate methods to chromosome **1q25–q31**, where mutations in a gene designated *CACP* (now *PRG4*) encoding a secreted proteoglycan were identified as the cause of the autosomal recessive syndrome (PMID: 10545950): "*we identified mutations in a gene (CACP) encoding a secreted proteoglycan as the cause of CACP.*" *PRG4* had previously been identified independently as the precursor of megakaryocyte-stimulating factor and as the articular cartilage "superficial zone protein," unifying several research threads under one gene.

Across subsequent case series the inheritance mechanism is uniform: **biallelic loss-of-function variants**. A large cohort of 13 Indian patients explicitly states the syndrome "*is caused by biallelic loss-of-function variants in PRG4*" (PMID: 38856641), and multiple independent reports describe homozygous truncating variants such as c.1290del (p.T431Lfs*481) in consanguineous families (PMID: 40874560).

Gene annotation: HGNC *PRG4*; OMIM gene 605602; OMIM phenotype 208250. Suggested MONDO: **MONDO:0008828**.

Finding 2 — Mechanism: lubricin lubricates cartilage AND restrains synovial overgrowth; its loss produces friction-driven chondrocyte apoptosis plus synovial hyperplasia

Lubricin has a **dual protective role**, and CACP pathology reflects the loss of both functions. In lubricin-mutant mice, abnormal protein deposits accumulate on the cartilage surface, superficial-zone chondrocytes are lost, and — critically — *"intimal cells in the synovium surrounding the joint space became hyperplastic, which further contributed to joint failure. Purified or recombinant lubricin inhibited the growth of these synoviocytes in vitro"* (PMID: 15719068). This single observation explains both the cartilage failure and the synovial hyperplasia that clinically mimics inflammatory arthritis.

The friction–apoptosis link is mechanistically demonstrated: lubricin-knockout joints show elevated whole-joint friction and increased chondrocyte apoptosis, and in a bovine cartilage-on-cartilage explant system *"we observed a direct correlation between coefficient of friction and chondrocyte apoptosis in the superficial layers of cartilage,"* an effect reversed by adding lubricin (PMID: 23530215). Downstream, friction induces chondrocyte **mitochondrial dysregulation and caspase-3 activation** (PMID: 28604608), identifying apoptosis as the terminal tissue-damage step.

Suggested GO/CL terms: GO:0006915 (apoptotic process), GO:0005615 (extracellular space), GO:0008285 (negative regulation of cell proliferation); CL:0000138 (chondrocyte), CL:0000214 (synovial cell).

Finding 3 — The clinical tetrad is non-inflammatory and is frequently misdiagnosed as JIA

CACP presents as a tetrad: congenital/early-onset **camptodactyly**, childhood-onset **non-inflammatory arthropathy with synovial hyperplasia**, progressive **coxa vara**, and non-inflammatory **pericardial (± pleural) effusion** (PMID: 40830943). Phenotype frequencies from the 13-patient Indian cohort are: *"Camptodactyly (13/13), coxa vara (11/13), short femoral neck (11/13) and arthritis in large joints (12/13)"* (PMID: 38856641), with wrists (11/13), ankles (11/13), elbows (10/13) and knees (10/13) most affected.

Because synovial hyperplasia superficially resembles inflammatory arthritis but **inflammatory markers are normal and synovial fluid is non-inflammatory (low WBC)**, misdiagnosis as JIA is the rule rather than the exception. In one series *"all patients were*

exposed to biologic therapy due to recalcitrant JIA" (PMID: 40475173), and multiple independent reports describe prolonged, ineffective immunosuppression before genetic confirmation (PMID: 41626297; PMID: 42074176; PMID: 42482035).

Suggested HPO terms: HP:0100490 (camptodactyly of finger), HP:0005750 (coxa vara), HP:0001367 (abnormal joint morphology), HP:0001644 (pericardial effusion), HP:0002102 (pleural effusion), HP:0100658 (joint effusion), HP:0100763 (synovial hypertrophy).

Finding 4 — Serosal (pericardial/pleural) involvement is variable, often later, and can be life-threatening

Pericarditis/pericardial effusion is the **most variable and least penetrant** element of the tetrad. It is described as occurring "*rarely*" in some cohorts (PMID: 40475173: "*early-onset camptodactyly, noninflammatory arthropathy, coxa vara deformity, and, rarely, pericardial effusion*"), reflecting lubricin's role on visceral serosal surfaces. When present and severe, it progresses to **constrictive pericarditis requiring pericardiectomy**, and has been misattributed to tuberculosis: "*the elder sister had pericardial effusion with constrictive pericarditis, underwent pericardiectomy and received empirical treatment for suspected tuberculosis*" (PMID: 38955384). Neonatal pleural effusion with respiratory distress followed by later pericardiectomy has also been reported (PMID: 40830943), and a unique association with **mitral stenosis** requiring commissurotomy was documented, hypothesized to relate to the proteoglycan content of the mitral valve (PMID: 38523390).

Finding 5 — No cure exists; management is supportive; rhPRG4 replacement is the rational investigational therapy

No approved disease-modifying treatment exists. Because the arthropathy is non-inflammatory, anti-inflammatory/immunosuppressive regimens fail: a patient "*despite receiving treatment modalities such as non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate, and corticosteroids... experienced minimal improvement*" (PMID: 40830943). The mechanistically rational strategy is **lubricin (rhPRG4) replacement**: intra-articular full-length recombinant human PRG4 reduced cartilage damage in a Yucatan minipig model of medial-meniscus destabilization — "*the rhPRG4 group had significantly less macroscopic cartilage damage in the medial tibial [plateau]*" (PMID: 28129516) — and purified/recombinant lubricin inhibits synoviocyte overgrowth and reduces chondrocyte apoptosis in vitro (PMID: 15719068; PMID: 23530215). Supportive care includes physiotherapy, orthopedic correction of coxa vara (e.g., valgus osteotomy), joint replacement for end-stage arthropathy, and pericardiectomy for constrictive pericarditis.

Suggested NCIT terms: NCIT:C15431 (Physical Therapy), NCIT:C15329 (Surgery), protein replacement therapy (rhPRG4, investigational).

Finding 6 — Mutational spectrum: predominantly truncating (frameshift/nonsense) loss-of-function variants, with strong consanguinity/homozygosity

As of 2023 only "36 pathogenic mutations have been reported in this gene" (PMID: 36694203), underscoring the disease's rarity. The spectrum is overwhelmingly **truncating**:

Variant	Type	Reference
c.1290del (p.T431Lfs*481)	Frameshift	PMID: 40874560
c.3756dup	Frameshift (duplication)	PMID: 41626297
c.2208del (p.Thr737ProfsTer175)	Frameshift	PMID: 42482035
c.4104T>A (p.Tyr1368Ter)	Nonsense	PMID: 42482035
c.3636G>T, c.1935del, c.1134dup, c.1699del, c.962T>A	5 novel	PMID: 38856641
c.2645_2646delGA; c.2883_2886delAAGA	Frameshift deletions	PMID: 25297354

The 13-patient Indian cohort reported "five novel disease-causing variants (c.3636G>T, c.1935del, c.1134dup, c.1699del and c.962T>A)" (PMID: 38856641). Variants are typically **homozygous in consanguineous families**, consistent with autosomal recessive inheritance. Most truncating variants are predicted to trigger **nonsense-mediated decay** or yield non-functional truncated protein (PMID: 40874560). Under ACMG/AMP these are generally classified pathogenic/likely pathogenic (null variant in a gene where LOF is the established mechanism).

Finding 7 — The *Prg4*-null mouse recapitulates key CACP features

The lubricin-deficient (*Prg4*^{-/-}) mouse is the primary disease model. Mice are viable and fertile with normal joints at birth, then develop age-dependent cartilage-surface protein deposits, superficial-zone chondrocyte loss, synovial intimal hyperplasia, and periarticular pathology: "tendon and tendon sheath involvement was present in the ankle joints, where morphologic changes and abnormal calcification of these structures were observed" (PMID: 15719068) — relevant to the camptodactyly/contracture phenotype. Stereological analysis confirms deficient superficial/upper-intermediate-zone chondrocyte cellularity with caspase-3/TUNEL-positive apoptosis (PMID: 26975998). In the temporomandibular joint, "as early as 2 weeks of age,

mutant mice exhibited hyperplasia in the glenoid fossa articular cartilage, articular disc, and synovial membrane" progressing to osteoarthritic degradation, ectopic cartilage, and mineralization (PMID: 24834922; PMID: 26945615; PMID: 26534931). Ectopic cartilage in *Prg4*-null TMJ discs is associated with **excess BMP signaling** and **ectopic hedgehog signaling**, candidate downstream pathways.

Finding 8 — Protein-level consequence: truncating mutations abolish lubricin synthesis/secretion; normal lubricin requires disulfide-dependent SPC processing

In patients carrying frameshift or nonsense *PRG4* mutations, *"the antiserum did not detect lubricin in synovial fluid or cultured synoviocytes from several patients with frameshift or nonsense mutations in PRG4"* (PMID: 16000300) — direct evidence that the disease mechanism is **loss of protein (absent synthesis/secretion)**. The same work showed that wild-type lubricin undergoes post-translational cleavage within its C-terminal hemopexin-like domain by a **subtilisin-like proprotein convertase (SPC)**, and that *"formation of an intrachain disulfide bond is required for SPC-mediated cleavage and that SPC-mediated cleavage is essential to protein function."* Epitope mapping localizes key monoclonal-antibody epitopes to O-linked oligosaccharides on the mucin-domain KEPAPTTT motif (PMID: 25642942).

Finding 9 — Diagnostic biomarker: lubricin is absent from blood and synovial fluid, enabling an antibody-based test alongside sequencing

Epitope-specific anti-lubricin monoclonal antibodies (raised in *Prg4*^{-/-} mice) detect lubricin in healthy individuals but not in CACP patients: *"the competition ELISA detected lubricin in blood samples from healthy individuals but not from patients with CACP, indicating blood can be used in a diagnostic test for patients suspected of having CACP"* (PMID: 25642942). This provides a **blood-based screening/confirmation assay**. Definitive diagnosis remains *PRG4* sequencing (WES/WGS/single-gene) (PMID: 38856641). Supporting distinguishing labs/imaging: normal ESR/CRP; non-inflammatory synovial fluid (gelatinous, viscous, low WBC, sterile — PMID: 41637065); musculoskeletal ultrasound shows marked synovial effusion and circumferential synovial hypertrophy **without power Doppler activity** (PMID: 41637065); radiographs show joint effusion/synovial debris without erosions, coxa vara, short femoral neck, and metaphyseal flaring (PMID: 42074176).

Finding 10 — Epidemiology/inheritance: ultra-rare autosomal recessive, consanguinity-linked, complete joint penetrance with variable expressivity, no strong sex bias

CACP is an ultra-rare monogenic autosomal recessive disorder (OMIM 208250) with **no established population prevalence**; only a few hundred cases and ~36 catalogued mutations are reported worldwide (PMID: 36694203). Cases cluster in **consanguineous families and populations** (Middle East, Turkey, South Asia, North Africa). The 13-patient cohort derived from "*eight consanguineous Indian families*" with 7 females and 6 males (PMID: 38856641), indicating **no strong sex predilection**. Penetrance of the joint phenotype is essentially complete in biallelic carriers, while **expressivity — especially the cardiac/serosal component — is variable**. Regionally, a Southeastern Turkey series identified CACP in 12 of 47 individuals evaluated for non-inflammatory musculoskeletal complaints mimicking rheumatic disease (PMID: 40626694), underscoring its relative frequency among genetic JIA mimics in consanguineous populations.

Finding 11 — Natural history/prognosis: congenital onset, chronic progressive non-inflammatory arthropathy; cardiac serositis is the main life-threatening risk; cognition and lifespan usually preserved

Onset is congenital/early (camptodactyly at birth/infancy; arthropathy in early childhood). The course is **chronic and progressive**: "*deficiency of PRG4 results in progressive worsening of joint deformity with age*" (PMID: 38856641), producing large-joint contractures, coxa vara/short femoral neck, and "*precocious joint failure*" (PMID: 15719068). Reduced bone mineral density has been reported as part of a broader phenotypic burden (PMID: 42482035). Serosal disease can present even in adulthood as a first episode of constrictive pericarditis and represents the principal cause of serious morbidity/mortality; most patients have **normal intelligence and near-normal lifespan when cardiac disease is managed**.

Mechanistic Model / Interpretation

Ordered causal chain (initiating lesion → clinical manifestation)

1. **Biallelic truncating mutation in PRG4** (frameshift/nonsense) **leads to** loss of full-length lubricin mRNA/protein via nonsense-mediated decay or non-functional truncated product

(demonstrated: lubricin undetectable in patient synovial fluid/synoviocytes,

P 16000300

2. Absent lubricin **results in** loss of boundary lubrication at articular cartilage and serosal surfaces, **and in parallel** loss of the normal inhibitory signal that restrains synovial intimal cell proliferation (demonstrated in mouse/in vitro,

P 15719068

→ **Branch A (cartilage/joint):** - 3a. Loss of lubrication **leads to** an elevated coefficient of friction at the cartilage surface (demonstrated,

P 23530215

28604608). - 4a. Increased friction **results in** superficial-zone chondrocyte mitochondrial dysregulation and caspase-3-mediated apoptosis, **leading to** depletion of superficial-zone chondrocytes and surface protein deposition (demonstrated,

P 23530215

P 26975998

P 28604608

- 5a. In parallel, de-repressed synovial intimal cells **undergo hyperplasia**, producing non-inflammatory synovial thickening and effusion (demonstrated,

P 15719068

- 6a. Progressive cartilage failure + synovial hyperplasia **leads to** precocious large-joint arthropathy, contractures (camptodactyly, inferred from tendon/sheath involvement), and, at the hip, coxa vara with short femoral neck (clinical,

P 38856641

P 15719068

→ **Branch B (serosa):** - 3b. Absent lubricin on pericardial/pleural serosal surfaces **leads to** non-inflammatory serosal effusion, **which can result in** fibrosis/constrictive pericarditis (clinical, variable expressivity;

P 40475173

P 38955384

Upstream vs downstream

- **Upstream (initiating):** *PRG4*-null genotype → absent lubricin protein.
- **Midstream (mechanistic):** increased friction + loss of synoviocyte growth inhibition.
- **Downstream (effector):** chondrocyte apoptosis, synovial hyperplasia, serosal effusion.
- **Terminal (clinical):** camptodactyly, arthropathy, coxa vara, pericarditis, reduced BMD.

Cell types, tissues, and compartments

Level	Entities	Suggested ontology
Cells	Superficial-zone chondrocyte; synovial intimal cell (synoviocyte)	CL:0000138; CL:0000214
Tissue	Articular cartilage, synovial membrane, tendon/sheath, pericardium, pleura	UBERON:0002418, 0002103, 0000043, 0002407, 0000977
Organ/system	Joints (hip, knee, wrist, ankle, elbow, fingers, TMJ), heart (pericardium), lung (pleura), skeleton (femoral neck)	Musculoskeletal + cardiovascular + respiratory
Subcellular	Extracellular space (secreted lubricin); chondrocyte mitochondria (apoptotic signaling)	GO:0005615; GO:0005739
Processes	Boundary lubrication, apoptotic process, negative regulation of cell proliferation	GO:0006915; GO:0008285

Mechanistic nuances

- CACP is **not inflammatory**: synovial hyperplasia is a direct consequence of lost lubricin growth-inhibition, not immune-driven synovitis — explaining the universal failure of immunosuppression and the normal CRP/ESR.

- Mouse models reveal **downstream signaling perturbations** (ectopic hedgehog and excess BMP signaling driving ectopic cartilage/osteophytes in the TMJ;

[P 26945615](#)

[P 26534931](#)

), which are candidate secondary pathways best characterized in the TMJ model rather than in human CACP tissue.

Evidence Base

PMID	Title (abbrev.)	Source type	Contribution
10545950	<i>CACP, encoding a secreted proteoglycan, is mutated in CACP</i>	Human genetics	Establishes <i>PRG4</i> as causal gene (positional cloning)
38856641	<i>Thirteen Indians with CACP syndrome</i>	Human cohort	Biallelic LOF; phenotype frequencies; 5 novel variants; progression
15719068	<i>Lubricin protects cartilage and inhibits synovial overgrowth</i>	Mouse / in vitro	Dual mechanism; precocious joint failure; tendon pathology
23530215	<i>Lubricin and prevention of chondrocyte apoptosis</i>	In vitro / mouse	Friction ↔ apoptosis causal link
28604608	<i>Friction-induced mitochondrial dysregulation in <i>Prg4</i> KO</i>	Mouse	Caspase-3/mitochondrial chondrocyte death
16000300	<i>Consequences of disease-causing mutations on lubricin</i>	In vitro / human	Truncating mutations abolish protein; SPC/disulfide processing
25642942	<i>Anti-lubricin monoclonal antibodies</i>	In vitro / human	Blood-based diagnostic assay (lubricin absent in CACP)
28129516	<i>Intra-articular rhPRG4 in Yucatan minipig</i>	Large-animal	Preclinical rationale for rhPRG4 replacement
40475173	<i>CACP caused by truncating mutations (JIA mimic)</i>	Human	Misdiagnosis as JIA; biologic exposure; pericarditis variable
40830943	<i>First Iranian CACP case</i>	Human	Tetrad; failure of NSAIDs/MTX/steroids; pleural effusion
38955384	<i>CACP syndrome review/cases</i>	Human	Constrictive pericarditis → pericardiectomy; TB misdiagnosis
38523390	<i>CACP with mitral stenosis</i>	Human	Rare cardiac valve association
36694203	<i>Novel <i>PRG4</i> mutation, two sisters</i>	Human	Quantifies ~36 known mutations (rarity)

PMID	Title (abbrev.)	Source type	Contribution
26975998	<i>Superficial-zone cellularity deficient in lubricin-null mice</i>	Mouse	Stereological chondrocyte loss + caspase-3
24834922	<i>Lubricin required for TMJ integrity</i>	Mouse	TMJ hyperplasia model recapitulation
26945615 / 26534931	<i>Ectopic hedgehog / excess BMP in Prg4-null TMJ</i>	Mouse	Downstream signaling pathways
41637065	<i>MSUS of CACP joints</i>	Human	Synovial hypertrophy/effusion without power Doppler; sterile fluid
42482035	<i>CACP with bone-health emphasis</i>	Human	Novel variants; reduced BMD; JIA mimic
40626694	<i>Genetic diseases mimicking rheumatic disorders (Turkey)</i>	Human	CACP among JIA mimics in consanguineous population
25297354	<i>Novel PRG4 mutations in Indian families</i>	Human	Early frameshift variants from India

Consistency: All human and model-organism evidence converges on a single, coherent loss-of-function mechanism. No source contradicts the core model; the main variability is clinical expressivity of the cardiac/serosal component.

Section-by-Section Compendium

1. Disease information. CACP (MONDO:0008828; OMIM 208250; ORPHA:1236). Synonyms: Camptodactyly-arthropathy-coxa vara-pericarditis syndrome; CACP syndrome; arthropathy-camptodactyly syndrome; familial arthropathy. Information is derived from **aggregated disease-level case reports/series and model-organism studies** (no large EHR datasets; the disease is ultra-rare).

2. Etiology. Purely **genetic** — biallelic LOF of *PRG4*. The principal non-genetic contributor is **consanguinity** (increases probability of homozygous inheritance). No environmental, infectious, toxic, or lifestyle causes; no known protective alleles or gene–environment interactions. Not applicable: GWAS loci, common susceptibility SNPs.

3. Phenotypes. Camptodactyly (congenital physical manifestation, ~100% — HP:0100490); non-inflammatory large-joint arthropathy with synovial hyperplasia (clinical sign, childhood onset, progressive, ~92–100% — HP:0100658/HP:0100763); coxa vara (radiographic, childhood, progressive, ~85% — HP:0005750); short femoral neck (~85%); pericardial effusion (variable onset, variable/less frequent — HP:0001644); pleural effusion (HP:0002102); reduced bone mineral density (HP:0004349). Labs: **normal ESR/CRP** (key distinguisher), non-inflammatory synovial fluid. Quality of life: progressive contractures and hip deformity impair mobility and daily functioning; cardiac tamponade/constriction is the severe-impact phenotype.

4. Genetic/molecular. Causal gene *PRG4* (HGNC:9361; 1q31.1; OMIM 605602). Variant classes: predominantly **frameshift and nonsense (truncating)**; ACMG class pathogenic/likely pathogenic; **germline, homozygous**; functional consequence **loss of function** (absent secreted protein). Allele frequencies: individually very rare/absent in gnomAD (private family mutations). No established modifier genes, disease-specific epigenetic signatures, or large chromosomal abnormalities.

5. Environmental. None causal. No toxins, infectious agents, or lifestyle factors. (Serosal effusions are sometimes clinically *mistaken* for tuberculous pericarditis — a diagnostic pitfall, not an etiology.)

6. Mechanism. See causal chain above. Core pathways: boundary-lubrication failure → friction → mitochondrial/caspase-3 apoptosis of superficial-zone chondrocytes; loss of synoviocyte growth suppression → hyperplasia; downstream ectopic hedgehog/BMP signaling in the model TMJ.

7. Anatomical structures. Primary: synovial joints (hip/coxa vara, knee, wrist, ankle, elbow, fingers, TMJ), articular cartilage, synovium, tendon sheaths. Secondary: pericardium, pleura (serosal), occasionally cardiac valves; skeleton (femoral neck, reduced BMD). Bilateral/symmetrical joint involvement. UBERON: 0002418 (cartilage), 0002103 (synovial membrane), 0000977 (pleura), 0002407 (pericardium).

8. Temporal development. Onset congenital (camptodactyly) → early childhood (arthropathy, coxa vara) → variable, sometimes adult-onset serosal disease. Course: chronic, progressive, non-remitting joint disease; serosal episodes may be episodic. Lifelong. The critical window for potential lubricin-replacement intervention is likely **early**, before irreversible cartilage loss.

9. Inheritance & population. Autosomal recessive; ultra-rare (no established prevalence); consanguinity-associated; complete joint penetrance, variable expressivity (cardiac); no strong sex bias; founder/private mutations in consanguineous families (South Asia, Middle East, Turkey, North Africa). Carrier frequency not established.

10. Diagnostics. Normal ESR/CRP; non-inflammatory, sterile, viscous synovial fluid; radiographs show effusion/synovial debris without erosions, coxa vara, short femoral neck, metaphyseal flaring; MSUS shows synovial hypertrophy/effusion without power Doppler; **lubricin absent on blood/synovial-fluid immunoassay; definitive = PRG4 sequencing (WES/WGS/single-gene).** Differential: JIA (key mimic), skeletal dysplasias (progressive pseudorheumatoid dysplasia, mucopolysaccharidoses), other familial arthropathies.

11. Prognosis. Progressive disability from joint deformity; constrictive pericarditis is the main mortality risk (manageable with pericardiectomy); normal cognition; near-normal lifespan with cardiac management. Main prognostic factor: presence/severity of cardiac involvement.

12. Treatment. No cure. Supportive: physiotherapy/occupational therapy, analgesia, orthopedic surgery (valgus osteotomy for coxa vara, joint replacement), pericardiectomy for constriction, valve surgery if indicated. Immunosuppressants/biologics are **ineffective** and should be discontinued once CACP is confirmed. Investigational: **rhPRG4 replacement** (preclinical). NCIT: physical therapy, orthopedic surgery, protein replacement therapy.

13. Prevention. No primary prevention. **Genetic counseling** and **carrier/cascade testing** in consanguineous families; **prenatal/preimplantation genetic testing** feasible once the familial variant is known. Tertiary prevention: regular echocardiographic surveillance for pericardial/valvular disease; bone-health monitoring (DXA).

14. Other species / natural disease. Orthologous gene: mouse *Prg4* (NCBI Gene 56689). The *Prg4*^{-/-} mouse is an engineered (not natural) model; no well-established spontaneous CACP-equivalent natural disease in companion animals is documented in this knowledge base. The lubricin boundary-lubrication mechanism is evolutionarily conserved across mammals (bovine, equine, porcine lubricin all studied).

15. Model organisms. Primary: **mouse** (*Prg4* knockout — mammalian genetic model) recapitulating synovial hyperplasia, superficial-zone chondrocyte loss/apoptosis, tendon/sheath pathology, and TMJ degeneration. Large-animal pharmacology: **Yucatan minipig** (rhPRG4 intra-articular efficacy). In vitro: bovine cartilage explants, synoviocyte cultures. Limitations: mice are born with normal joints and develop disease postnatally (age-dependent), and the human cardiac/serosal phenotype is not a prominent reported feature of the mouse. Resource: MGI (*Prg4*).

Limitations and Knowledge Gaps

1. **No epidemiological denominator.** Prevalence/incidence, carrier frequency, and population-specific rates are unknown; all data derive from small case series biased toward consanguineous populations.
 2. **Cardiac mechanism under-characterized.** Why serosal/pericardial involvement is variable and sometimes adult-onset — and the basis of the rare mitral-valve association — is not mechanistically established.
 3. **Weak genotype–phenotype correlation.** With predominantly null alleles, the determinants of variable expressivity (modifier genes, environment) are unknown.
 4. **rhPRG4 is preclinical only** for CACP; no human CACP clinical-trial outcome data (NCT identifiers) were identified in this investigation.
 5. **Mouse-model gaps.** The knockout does not clearly reproduce human cardiac serositis; camptodactyly is inferred from tendon-sheath pathology rather than directly modeled.
 6. **No omics in CACP patients.** Patient transcriptomic/proteomic/metabolomic profiling is largely absent; mechanistic signaling data (hedgehog/BMP) derive from the TMJ mouse model, not human CACP tissue.
 7. **Bone-health phenotype newly emerging.** Reduced BMD is reported in isolated cases ([PMID: 42482035](#)) but frequency and mechanism are undefined.
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Proposed Follow-up Experiments / Actions

1. **Establish an international CACP registry / natural-history cohort** to define prevalence, phenotype frequencies (especially cardiac penetrance by age), and progression rates.
2. **Advance rhPRG4 toward a first-in-human CACP trial** — intra-articular dosing informed by minipig data ([PMID: 28129516](#)); define outcome measures (MSUS synovial hypertrophy, friction surrogates, joint function).
3. **Validate the lubricin blood immunoassay** ([PMID: 25642942](#)) as a first-line, low-cost diagnostic screen to shorten the diagnostic odyssey and curb inappropriate biologic use.

4. **Deploy early *PRG4* sequencing** in any child with non-inflammatory, immunosuppression-refractory arthritis plus normal CRP/ESR and/or coxa vara — codify this as a diagnostic pathway/guideline.
 5. **Interrogate downstream signaling (hedgehog/BMP)** in human CACP synovium/cartilage to test whether pathway inhibitors (e.g., BMP-receptor kinase inhibitors) could serve as adjunct therapies, building on TMJ-model findings ([PMID: 26534931](#)).
 6. **Systematically assess cardiac and bone health** (serial echocardiography; DXA) across cohorts to quantify constrictive-pericarditis risk and the newly reported low-BMD phenotype.
 7. **Explore gene/cell-based correction** (AAV *PRG4* delivery, or lubricin-secreting cell therapy) as a durable alternative to repeated protein replacement.
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Report compiled from 11 confirmed findings and 37 reviewed publications over 5 investigation iterations. Evidence types are indicated per citation (human clinical, mouse/model organism, in vitro, large-animal preclinical). Primary literature PMIDs are provided throughout; direct abstract quotes are used verbatim to support key mechanistic and clinical claims.
