Oculofaciocardiodental (OFCD) Syndrome: A Comprehensive Disease Characteristics Report

Disease: Oculofaciocardiodental Syndrome **OMIM:** 300166 · **Orphanet:** ORPHA:2712 · **MONDO:** 0010588 · **Category:** Mendelian (X-linked dominant, male-lethal) **Causal gene:** *BCOR* (BCL6 corepressor), Xp11.4

Summary

Oculofaciocardiodental (OFCD) syndrome is an ultra-rare X-linked dominant, presumptively male-lethal multiple congenital anomaly disorder caused by germline **loss-of-function (null/truncating) mutations in *BCOR***, the gene encoding the BCL6 corepressor located at Xp11.4. The condition is defined clinically by a diagnostic tetrad reflected in its name — **ocular** (congenital cataract, microphthalmia, secondary glaucoma), **facial** (dysmorphism: long narrow face, high nasal bridge, broad/bifid nose, cleft palate), **cardiac** (atrial/ventricular septal defects, valvular anomalies, laterality defects/dextrocardia), and **dental** anomalies — with **radiculomegaly of the canines (root gigantism)** serving as the pathognomonic sign that frequently brings these patients to clinical attention through dentistry. Fewer than a few hundred cases have been documented worldwide, and the disorder is chronically underrecognized.

Mechanistically, BCOR is a defining subunit of the non-canonical **Polycomb repressive complex 1.1 (PRC1.1)** — together with RING1B/RNF2, PCGF1, and KDM2B — which is recruited to nonmethylated CpG islands to remove H3K36me2 and deposit repressive H2A monoubiquitylation. Loss of BCOR function produces at least **two well-characterized, tissue-specific causal chains**. In dental mesenchymal stem cells, BCOR loss derepresses **AP-2α (TFAP2A)** and increases activating histone marks (H3K4/H3K36 methylation), enhancing osteo-/dentinogenic potential and driving the pathognomonic radiculomegaly; nonsense-mediated mRNA decay (NMD) of premature-termination-codon *BCOR* transcripts (via UPF1) modulates BMP2 and is integral to this phenotype. In the left lateral plate mesoderm, the

BCL6–BCOR complex normally restrains Notch signaling; its loss permits uncontrolled Notch activity, ESR1/HDAC1-mediated silencing of *Pitx2*, and consequent cardiac and laterality defects.

A key genotype–phenotype dosage rule emerges: **null *BCOR* alleles cause female OFCD (lethal in hemizygous males)**, whereas the **hypomorphic missense variant c.254C>T (p.Pro85Leu)** produces the allelic, milder **male X-linked recessive Lenz microphthalmia syndrome**. The phenotypic spectrum has expanded to include neurological features, pituitary/brain abnormalities, and an emerging tumor-predisposition dimension (lymphoma, insulinomas), consistent with BCOR's known tumor-suppressor role in leukemias and sarcomas. No disease-modifying therapy exists; management is symptomatic, multidisciplinary, and accompanied by genetic counseling for X-linked reproductive risk.

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1. Disease Information

Overview. OFCD syndrome is a rare X-linked dominant developmental disorder affecting the eyes, face, heart, and teeth. It was first described by Hayward in 1980 and is characterized by congenital cataracts, dysmorphic facial features, congenital heart disease, and distinctive dental abnormalities, most notably **radiculomegaly (root gigantism) of the canines**, which is pathognomonic (PMID: 30484210; PMID: 23827343). It is frequently unrecognized by medical and dental professionals, and historically only ~20 cases were reported, though the count has grown with molecular diagnosis (PMID: 19093058).

Key identifiers.

Resource	Identifier
OMIM	300166
Orphanet	ORPHA:2712
MONDO	MONDO:0010588
Gene (HGNC)	*BCOR* (HGNC:20893), Xp11.4
MeSH	Oculofaciocardiodental syndrome / Microphthalmia (associated)

Synonyms / alternative names. OFCD syndrome; Oculo-facio-cardio-dental syndrome; MCOPS2 (in the microphthalmia syndromic series); part of the "X-linked microphthalmia" spectrum allelic with **Lenz microphthalmia syndrome (MAA2)**.

Information source. Disease-level knowledge derives predominantly from **aggregated resources (OMIM, Orphanet)** and from **individual patient case reports/small family series** rather than large EHR datasets, reflecting the disorder's rarity.

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2. Etiology

Primary cause — genetic. OFCD is a monogenic Mendelian disorder caused by **germline loss-of-function mutations in *BCOR***. Ng et al. (2004) identified frameshift, deletion, and nonsense mutations in *BCOR* across seven OFCD families, establishing null *BCOR* alleles as causal (PMID: 15004558):

> "we found different frameshift, deletion and nonsense mutations in BCOR in seven families affected with OFCD"

Subsequent cohorts confirmed *BCOR* as the sole molecular cause (PMID: 15770227; PMID: 19367324):

> "Our data confirm that BCOR is the causative gene for OFCD syndrome" (PMID: 15770227)

Genetic risk factors. The only established risk factor is possession of a pathogenic *BCOR* null allele. Nearly all reported OFCD variants create premature termination codons subject to NMD. There are no known common susceptibility loci or polygenic contributions; this is a fully penetrant Mendelian condition rather than a complex trait.

Environmental / infectious risk factors. None identified. No toxins, teratogens, lifestyle factors, or infectious agents are implicated in OFCD causation. As a germline single-gene disorder, environmental modifiers are not established.

Protective factors. None known at the genetic or environmental level. The principal biological "modifier" of severity is **X-inactivation mosaicism** in heterozygous females — skewed inactivation favoring the wild-type allele can yield mild or nearly asymptomatic carriers (PMID: 19367324).

Gene–environment interactions. Not applicable/established; OFCD is driven by intrinsic developmental gene dosage rather than gene–environment interplay.

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3. Phenotypes

OFCD phenotypes are congenital physical malformations and structural anomalies. The four cardinal domains and representative HPO terms:

Domain	Features	Frequency	Suggested HPO
Ocular	Congenital cataract (near-universal), microphthalmia, microcornea, secondary/ congenital glaucoma, persistent fetal vasculature, foveal photoreceptor atrophy	Cataract ~universal; others variable	HP:0000518 (Cataract), HP:0000568 (Microphthalmia), HP:0000501 (Glaucoma), HP:0000482 (Microcornea)
Facial	Long narrow face, high nasal bridge, broad/pointed/bifid nose, cleft palate/submucous cleft, ear anomalies	Common, variable	HP:0000278 (Long face), HP:0000426 (Prominent nasal bridge), HP:0000175 (Cleft palate), HP:0000453 (Bifid nose)
Cardiac	Atrial septal defect, ventricular septal defect, mitral valve anomalies/regurgitation, patent ductus arteriosus, laterality defects/dextrocardia	Common	HP:0001631 (ASD), HP:0001629 (VSD), HP:0001633 (Abnormal mitral valve), HP:0001651 (Dextrocardia)
Dental	**Radiculomegaly of canines (pathognomonic)**, oligodontia/ tooth agenesis, delayed eruption, persistent deciduous teeth, malocclusion (Class III), open apices	Radiculomegaly frequent in permanent dentition	HP:0000705 (Abnormal dental root morphology), HP:0000670 (Oligodontia), HP:0006335 (Delayed eruption of teeth)

Radiculomegaly characteristics. This is the defining sign. Affected canine roots reach extreme lengths — e.g., a mandibular canine of 47.5 mm (PMID: 20825507) and 38.0 mm calculated at **+14.8 SD** above normal (PMID: 30544426). Novel radiographic features include calcified dental papillae beneath open apices and pulp-stone-like calcifications; radiculomegaly develops progressively over years and is confirmed on orthopantomogram/CBCT (PMID: 30544426). In one Czech series, radiculomegaly occurred in 3/5 patients with permanent teeth, with additional agenesis, cleft lip/palate, and Class III malocclusion (PMID: 39438869).

Expanded phenotype. Ragge et al. (2019) broadened OFCD to include neuropathy, muscle hypotonia, pituitary underdevelopment, brain atrophy, lipoma, and the first description of childhood lymphoma (PMID: 29974297):

> "broaden the phenotypic description for OFCD to include neuropathy, muscle hypotonia, pituitary underdevelopment, brain atrophy, lipoma and the first description of childhood lymphoma in an OFCD case"

Skeletal features include 2nd–3rd toe syndactyly and radioulnar synostosis (PMID: 22301464; PMID: 19367324).

Onset, severity, progression. Onset is **congenital**. Severity is **variable** (X-inactivation-dependent in females), ranging from mild/underdiagnosed to multi-system. Structural malformations are **stable** post-development, but radiculomegaly is **progressive** through dental maturation, and glaucoma may progress.

Quality-of-life impact. Substantial: potential blindness from cataract/glaucoma, cardiac morbidity, chronic complex dental/orthodontic needs, facial dysmorphism with psychosocial impact, and variable neurodevelopmental involvement. Formal EQ-5D/SF-36 data are not available for this ultra-rare condition.

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4. Genetic / Molecular Information

Causal gene. ***BCOR*** (BCL6 corepressor), Xp11.4, OMIM *300485. Sole cause of OFCD (PMID: 15004558; PMID: 19367324).

Variant types. Predominantly **truncating/null**: frameshift, nonsense, and deletion variants creating premature termination codons. Reported examples include c.2382del p.(Lys795Argfs*12) and c.3914dup p.(Gln1306Alafs*20) (PMID: 39438869); c.888delG p.(Asn297Ilefs*80) (PMID: 22301464); c.3668delC (PMID: 38244688); c.265G>A (PMID: 30544426); intron-11 deletions (PMID: 38178193). Most are **de novo** or **transmitted from affected mothers**.

Variant classification. Reported pathogenic OFCD variants are classified **pathogenic/likely pathogenic** per ACMG/AMP, largely by loss-of-function mechanism (PVS1) plus segregation/de novo criteria.

Allele frequency. OFCD-causing variants are private/absent from population databases (gnomAD); *BCOR* loss-of-function is strongly constrained.

Somatic vs germline. OFCD is **germline**. Notably, **somatic** *BCOR*/*BCORL1* inactivating mutations occur in acute myeloid leukemia, myelodysplastic syndrome, and various sarcomas (PMID: 24515802) — a mechanistic bridge to the emerging tumor-predisposition dimension in germline cases:

> "inactivating somatic BCOR and BCORL1 mutations in patients with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS)"

Functional consequence. Loss of function, largely mediated by **NMD** of PTC-containing transcripts. Critically, both the OFCD-mutant truncated form and the Lenz p.P85L form retain the ability to interact with BCL6 and repress transcription, implicating **defects in alternative BCOR functions** rather than simple loss of BCL6 corepression (PMID: 15004558):

> "BCOR P85L and an OFCD-mutant form of BCOR can interact with BCL-6 and efficiently repress transcription"

Genotype–phenotype dosage rule (Finding F007). Null alleles → **female OFCD** (male-lethal); hypomorphic missense **p.Pro85Leu → male Lenz microphthalmia** (PMID: 29974297):

> "OFCD is an X-linked dominant syndrome caused by a variety of BCOR null mutations" … "is caused by hypomorphic BCOR variants, mainly by a specific missense variant c.254C > T, p.(Pro85Leu)"

Modifier genes. No classical modifier genes established. **X-inactivation skewing** is the dominant modifier of expressivity in females. A reported case with co-occurring *BCOR* and *MYLK* variants (multilocus pathogenic variation) altered surgical/cardiovascular risk stratification (PMID: 41236190).

Epigenetic information. *BCOR* itself acts through chromatin: loss increases activating H3K4/H3K36 methylation and reduces repressive H2A ubiquitylation at target loci (see Section 6). Disease-specific DNA methylation signatures are not established.

Chromosomal abnormalities. OFCD is typically a point/small-indel disorder, but genomic rearrangements at Xp have been reported alongside *BCOR* variants, including microduplications at Xp22.2-22.13 (involving *NHS*) and Xp21.3 (PMID: 22301464).

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5. Environmental Information

Not applicable. OFCD is a germline monogenic disorder. No environmental toxins, radiation, pollution, occupational exposures, lifestyle/behavioral factors, or infectious agents are known to cause or trigger it. This section is included for completeness and to signal a genuine negative.

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6. Mechanism / Pathophysiology

OFCD pathophysiology centers on loss of BCOR, a **PRC1.1** subunit, producing tissue-specific transcriptional derepression via two principal causal chains.

BCOR and PRC1.1 (Finding F004)

BCOR nucleates the non-canonical Polycomb complex **PRC1.1**, comprising **RING1B/RNF2, PCGF1, and KDM2B**, recruited to nonmethylated CpG islands (PMID: 24515802):

> "The BCL6 corepressor (BCOR) complex comprises ring finger protein 1B (RNF2/RING1B), polycomb group ring finger 1 (PCGF1), and lysine-specific demethylase 2B (KDM2B) and is uniquely recruited to nonmethylated CpG islands, where it removes histone H3K36me2 and induces repressive histone H2A monoubiquitylation"

Mouse work confirms BCOR/PRC1.1 developmental roles; conditional deletion recapitulates OFCD features (cleft palate/mandibular hypoplasia via neural crest; syndactyly via lateral mesoderm) (PMID: 32692983):

> "BCOR associates with Polycomb group proteins to form one subfamily of the diverse Polycomb repressive complex 1 (PRC1) complexes, designated PRC1.1"

GO terms: GO:0031519 (PcG protein complex), GO:0006355 (regulation of transcription, DNA-templated), GO:0016575 (histone deacetylation), GO:0035518 (histone H2A monoubiquitination), GO:0000122 (negative regulation of transcription by RNA Pol II).

Causal chain 1 — Dental radiculomegaly via AP-2α derepression (Finding F003)

Fan et al. (2009, *Nat Cell Biol*) showed OFCD-patient mesenchymal stem cells (MSCs) with *BCOR* mutation have increased osteo-/dentinogenic potential. **AP-2α (TFAP2A)** is a repressive BCOR target abnormally activated on *BCOR* loss (PMID: 19578371):

> "AP-2alpha was identified as a repressive target of BCOR, and BCOR mutation resulted in abnormal activation of AP-2alpha" "BCOR mutation increased histone H3K4 and H3K36 methylation in MSCs, thereby reactivating transcription of silenced target genes"

NMD adds a regulatory layer: UPF1 binds PTC-containing *BCOR* transcripts; UPF1 knockdown upregulates *BCOR*, and mutant *BCOR* alters **BMP2** in periodontal ligament cells (PMID: 38244688).

Causal chain: *BCOR* null → NMD/loss of PRC1.1 repression → ↑H3K4/H3K36me + ↓H2Aub at MSC targets → derepression of AP-2α (and altered BMP2) → enhanced osteo-/dentinogenesis → **canine radiculomegaly**.

Causal chain 2 — Cardiac/laterality defects via Notch–Pitx2 (Finding F006)

The **BCL6–BCOR complex normally restrains Notch signaling**. Sakano et al. (2010, *Genes Dev*) showed BCL6 forms a complex with BCOR on Notch-target promoters (e.g., *ESR1*/Enhancer of split related 1) and competes with the Notch1 intracellular domain, excluding coactivator Mastermind-like1 (PMID: 20230751):

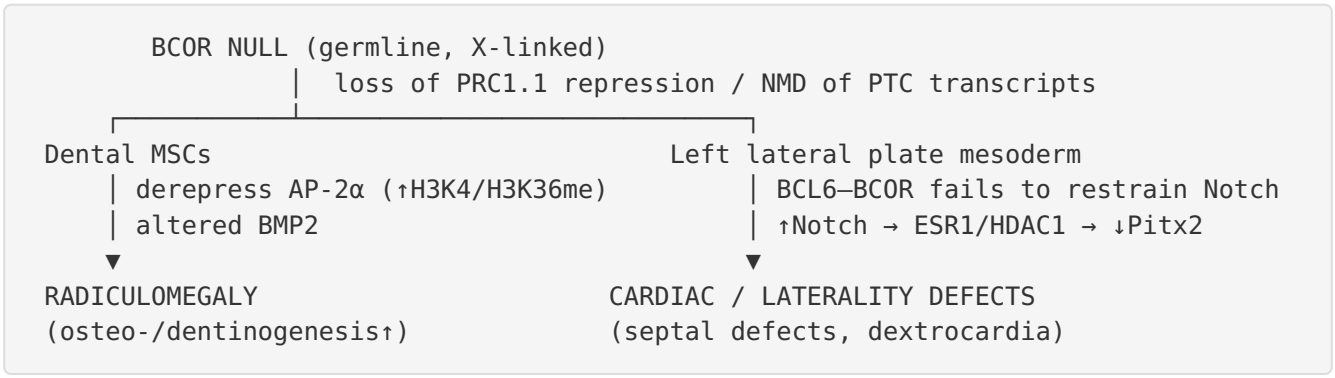
> "BCL6 forms a complex with BCL6 corepressor (BCoR) on the promoters of selected Notch target genes such as enhancer of split related 1. BCL6 also inhibits the transcription of these genes by competing for the Notch1 intracellular domain, preventing the coactivator Mastermind-like1 (MAM1) from binding"

Tanaka et al. (2014) linked this to laterality: ESR1 (downstream of Notch) represses *Pitx2* by binding the left-side ASE enhancer and recruiting HDAC1, blocking p300 (PMID: 24440151):

> "uncontrolled Notch activity in the left LPM caused by dysfunction of BCOR may result in cardiac/laterality defects of OFCD syndrome"

Causal chain: *BCOR* null → BCL6–BCOR fails to restrain Notch in left lateral plate mesoderm → uncontrolled Notch/ESR1–HDAC1 activity → **silencing of *Pitx2*** → disrupted left–right patterning → **septal defects, valve anomalies, dextrocardia/laterality defects**. Consistent with the human male case showing dextrocardia (PMID: 26196063).

Upstream vs downstream summary



Neoplasia dimension. BCOR's tumor-suppressor role (somatic inactivation in AML/MDS/sarcomas; PMID: 24515802) plausibly underlies germline OFCD tumor reports — childhood lymphoma (PMID: 29974297) and metachronous multiple insulinomas (PMID: 42324136).

Cell types (CL) / compartments (GO CC): mesenchymal stem cell (CL:0000134), periodontal ligament fibroblast, odontoblast (CL:0000060), neural crest cell (CL:0000333); nucleus/chromatin (GO:0005634 nucleus, GO:0000785 chromatin). **CHEBI:** BMP2 (protein), estrogen/ESR1 signaling.

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7. Anatomical Structures Affected

Organ level (primary): eye/lens (UBERON:0000019 eye; UBERON:0000965 lens), heart (UBERON:0000948), teeth/canine (UBERON:0001091 tooth), craniofacial skeleton (UBERON:0010363). **Secondary/other:** brain (UBERON:0000955), pituitary (UBERON:0000007), skeleton (hand/foot — syndactyly, radioulnar synostosis), pancreas (endocrine, insulinoma).

Body systems: visual, cardiovascular, craniofacial/skeletal, dental/stomatognathic, nervous, endocrine.

Tissue/cell level: dental mesenchymal stem cells and periodontal ligament (radiculomegaly); neural crest-derived craniofacial mesenchyme (cleft palate, mandibular hypoplasia); lateral plate mesoderm (cardiac/laterality, syndactyly); lens epithelium (cataract). CL terms as in Section 6.

Subcellular: nucleus/chromatin (site of PRC1.1 action, GO:0005634).

Localization / lateralization: Ocular and dental findings are typically **bilateral**; cardiac laterality defects are intrinsically **asymmetric** (dextrocardia, situs abnormalities).

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8. Temporal Development

- **Onset:** Congenital; ocular (cataract) and cardiac malformations present at/near birth. Dental radiculomegaly manifests and progresses through childhood/adolescence as the permanent dentition develops.
- **Onset pattern:** Chronic/developmental (structural malformations arise in utero).
- **Progression:** Structural malformations are stable after development; **radiculomegaly is progressive** over years (PMID: 30544426, 30-year longitudinal follow-up); glaucoma may be progressive and vision-threatening.
- **Course:** Chronic, lifelong; not episodic or relapsing–remitting.
- **Critical periods:** Embryonic organogenesis (eye, heart, left–right patterning) is the window of vulnerability; postnatal windows matter for cataract/glaucoma surgery timing and orthodontic intervention before radiculomegaly completion.

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9. Inheritance and Population

Inheritance. X-linked dominant with presumed **male lethality** (PMID: 15004558):

> "Oculofaciocardiodental syndrome (OFCD; OMIM 300166) is inherited in an X-linked dominant pattern with presumed male lethality"

Mouse models confirm male lethality — *Bcor* hemizygous null males die by ~E9.5, while heterozygous mosaic females show OFCD-like defects (PMID: 32692983):

> "Bcor hemizygosity in the entire male embryo resulted in embryonic lethality by E9.5"

Penetrance/expressivity. High penetrance in females but **highly variable expressivity**, governed by X-inactivation. Mosaic/skewed females may be mild or asymptomatic (PMID: 19367324).

Mosaicism. Somatic/germline mosaic *BCOR* mutations documented in females, including asymptomatic carriers (PMID: 19367324).

Rare males. Males with *BCOR* variants are exceptional (e.g., missense p.R540Q with dextrocardia; PMID: 26196063); hypomorphic p.P85L males present as Lenz microphthalmia rather than OFCD.

Epidemiology. Ultra-rare; prevalence not precisely established (Orphanet: <1/1,000,000). Historically ~20–40 reported cases, expanding with molecular testing (PMID: 19093058; PMID: 22449596). No founder effects, consanguinity role (dominant), or ethnic predilection established; cases reported worldwide (Korea, Vietnam, Czech Republic, Japan, etc.).

Sex ratio. Overwhelmingly **female** due to male lethality.

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10. Diagnostics

Clinical/radiographic. Diagnosis is often triggered by **canine radiculomegaly** on orthopantomogram/CBCT — pathognomonic and detectable by dentists (PMID: 30484210; PMID: 30544426). Ophthalmologic exam (cataract, microphthalmia, glaucoma, and posterior-segment findings such as persistent fetal vasculature and foveal photoreceptor atrophy on multimodal imaging; PMID: 38699441) and echocardiography (septal defects, valve anomalies, laterality) complete the workup.

Genetic testing (confirmatory). Single-gene *BCOR* sequencing or **exome/trio exome sequencing** is the diagnostic standard, validated by Sanger sequencing and segregation analysis (PMID: 39438869; PMID: 41236190). **Chromosomal microarray/CNV analysis** detects deletions/duplications and associated Xp rearrangements (PMID: 22301464). WES/WGS also enables detection of multilocus pathogenic variation (e.g., co-occurring *MYLK*) with clinical consequences (PMID: 41236190).

Diagnostic criteria. Core triad emphasized: **congenital cataract, microphthalmia, and radiculomegaly**, plus examination for skeletal defects (radioulnar synostosis) and cardiac/laterality defects (PMID: 19367324).

Differential diagnosis. Lenz microphthalmia syndrome (allelic; male, hypomorphic *BCOR*); Nance-Horan syndrome (*NHS*, overlapping ocular/dental features); other syndromic microphthalmia (SOX2, OTX2, STRA6, BMP4, HCCS, SMOC1) (PMID: 22005280).

Screening. Any patient with **congenital cataract plus dental abnormalities (radiculomegaly)** — even without family history — should be referred for genetic testing (PMID: 39438869). Cascade testing in families; prenatal/preimplantation testing feasible once a familial variant is known.

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11. Outcome / Prognosis

Survival. In affected females, life expectancy is generally near-normal, dominated by cardiac severity and surgical complications; hemizygous males are typically not viable (embryonic lethality). No formal survival statistics exist for this ultra-rare condition.

Morbidity / function. Chief morbidities: **visual impairment/blindness** (cataract, glaucoma, posterior-segment atrophy), **cardiac disease** (septal/valvular/laterality), lifelong **dental/orthodontic** burden, facial dysmorphism, and variable neurodevelopmental involvement (hypotonia, neuropathy, brain/pituitary abnormalities; PMID: 29974297).

Complications. Dental abscess from radiculomegalous teeth (PMID: 38178193); glaucoma; cardiac sequelae; emerging **tumor risk** — childhood lymphoma (PMID: 29974297) and metachronous insulinomas requiring repeated surgery (PMID: 42324136).

Prognostic factors. Degree of X-inactivation skewing (expressivity), cardiac defect severity, glaucoma control, and presence of additional pathogenic variants (MPV) that raise surgical risk (PMID: 41236190). No validated molecular prognostic biomarkers.

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12. Treatment

No disease-modifying/curative therapy exists. Management is **symptomatic, organ-directed, and multidisciplinary**.

Domain	Interventions	NCIT suggestion
Ocular	Cataract extraction / lensectomy with anterior vitrectomy & posterior capsulotomy; glaucoma surgery; visual rehabilitation	NCIT:C15277 (Ophthalmologic surgery)
Cardiac	Surgical/interventional repair of septal defects and valve anomalies; PDA closure	NCIT:C157769 (Cardiac surgery)
Dental	Endodontic (root canal) management of radiculomegalous teeth; extractions; surgical-orthodontic treatment with light forces to avoid ankylosis	NCIT:C15855 (Orthodontics); NCIT:C15329 (Endodontic therapy)
Craniofacial	Cleft palate repair; orthognathic surgery for Class III malocclusion	NCIT:C51823 (Orthognathic surgery)
Oncologic	Surgical resection of insulinomas; surveillance/ treatment of lymphoma	NCIT:C15329
Genetic	Genetic counseling for X-linked reproductive risk	NCIT:C15417 (Genetic counseling)

Endodontic treatment of radiculomegalous canines is technically challenging (extreme root length, multiple canals) (PMID: 20825507). Surgical-orthodontic therapy can effectively correct skeletal disharmony and improve occlusion/function (PMID: 22449596). Perioperative planning must integrate cardiac risk, and evolving genomic findings (e.g., *MYLK*) may alter surgical decision-making (PMID: 41236190).

Pharmacogenomics / advanced therapeutics (gene, cell, RNA-based, targeted, immuno). None established or approved for OFCD. No experimental clinical trials with NCT identifiers are documented for this condition.

13. Prevention

- **Primary prevention:** Not applicable (germline congenital disorder); no vaccination or risk-factor modification.
- **Secondary prevention / early detection:** High index of suspicion in any child with **congenital cataract** + **radiculomegaly/dental anomalies** → early referral for genetic

testing and specialized dental care (PMID: 39438869). Early ophthalmologic and cardiac evaluation improves outcomes.

- **Tertiary prevention:** Timely cataract/glaucoma surgery to preserve vision; cardiac repair; ongoing dental surveillance; **tumor surveillance** given emerging lymphoma/insulinoma associations (PMID: 42324136).
- **Genetic counseling:** Central to prevention — X-linked dominant with male lethality; discuss recurrence risk, prenatal/preimplantation testing, and cascade testing of at-risk female relatives.

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14. Other Species / Natural Disease

- **Taxonomy / orthologs:** *BCOR* is conserved; mouse *Bcor* (NCBI Gene 71458) and *Xenopus bcor* are the key experimental orthologs.
- **Model organism disease:** Mouse *Bcor* null recapitulates key OFCD/PRC1.1 developmental defects with male lethality (PMID: 32692983); *Xenopus* studies established the laterality/Notch–Pitx2 role (PMID: 20230751; PMID: 24440151).
- **Natural veterinary disease:** No naturally occurring OFCD-equivalent syndrome is documented in companion animals or wildlife (OMIA); this is a genuine gap.
- **Evolutionary conservation:** BCOR/PRC1.1 chromatin functions and left–right patterning via Notch–Pitx2 are deeply conserved across vertebrates, supporting cross-species mechanistic translation.
- **Zoonotic potential:** Not applicable.

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15. Model Organisms

Model	Type	Contribution / phenotype recapitulation
Mouse (*Bcor*)	Mammalian; conditional/tissue-specific knockout alleles	Male embryonic lethality by ~E9.5; heterozygous mosaic females show OFCD-like defects. Tissue-specific deletion recapitulates cleft palate/mandibular hypoplasia (neural crest) and syndactyly (lateral mesoderm), defining PRC1.1 developmental roles (PMID: 32692983)
Xenopus	Vertebrate embryo	Established BCOR requirement for left–right patterning; BCL6–BCOR restrains Notch to maintain Pitx2 in left LPM (PMID: 20230751; PMID: 24440151)
Human patient MSCs / periodontal ligament cells	In vitro / primary cells	Direct mechanistic dissection of radiculomegaly: AP-2α derepression, H3K4/H3K36 methylation increases, UPF1/NMD–BMP2 axis (PMID: 19578371; PMID: 38244688)

Model limitations. Complete male knockouts are embryonic-lethal, requiring conditional/mosaic strategies; no single model reproduces the full human ocular–facial–cardiac–dental tetrad simultaneously. Radiculomegaly (a human dental-specific phenotype) is best studied in patient-derived cells rather than rodent teeth.

Resources: MGI (mouse *Bcor*), Xenbase, Alliance of Genome Resources.

Mechanistic Model / Interpretation

OFCD is fundamentally a **chromatin/Polycomb dosage disorder**. A single functional dose of BCOR is required for normal development; its loss removes PRC1.1-mediated repression at CpG-island targets in specific progenitor populations, unleashing tissue-specific transcriptional programs. Two mechanistically independent but conceptually unified derepression events explain the two most distinctive features:

1. **AP-2α derepression in dental MSCs → radiculomegaly** (enhanced osteo-/dentinogenesis; modulated by NMD/UPF1 and BMP2).

2. **Notch de-restraint in left LPM → ESR1/HDAC1 silencing of Pitx2 → cardiac/laterality defects.**

The **dosage/allele-class rule** unifies OFCD and Lenz microphthalmia into one BCOR spectrum: **null alleles → female OFCD (male-lethal)**; **hypomorphic p.P85L → male Lenz**. Because both allele classes retain BCL6 binding and repression, the pathogenic defect lies in **alternative, dose-sensitive BCOR/PRC1.1 functions**. Finally, BCOR's somatic tumor-suppressor role rationalizes the emerging neoplasia dimension (lymphoma, insulinoma) in germline patients.

Evidence Base

PMID	Title (abbrev.)	Support
15004558	OFCD and Lenz result from distinct BCOR mutation classes	Null → OFCD; P85L → Lenz; both retain BCL6 repression; X-linked male lethality
15770227	Novel BCOR mutations in OFCD	Confirms BCOR as sole cause
19367324	BCOR analysis across OFCD/Lenz/ laterality	Female OFCD null cohort; mosaicism; diagnostic criteria
19578371	BCOR regulates MSC function epigenetically	Radiculomegaly mechanism: AP-2α, H3K4/ H3K36me
38244688	NMD/UPF1 in OFCD root formation	UPF1–BCOR–BMP2 axis in radiculomegaly
24515802	Polycomb disruption in cancers	PRC1.1 composition; somatic BCOR in AML/ MDS
32692983	Conditional Bcor PRC1.1 mouse	Male lethality E9.5; OFCD-like tissue defects
20230751	BCL6 canalizes Notch transcription	BCL6–BCOR restrains Notch (Xenopus LR patterning)
24440151	Molecular pathogenesis of cardiac/ laterality defects	Notch→ESR1/HDAC1→Pitx2 chain
29974297	Expanding BCOR microphthalmia phenotype	Neuro/pituitary/lymphoma expansion; null vs P85L rule
26196063	Male BCOR case with dextrocardia	Human laterality confirmation
42324136	Metachronous insulinomas in OFCD	Tumor predisposition dimension
41236190	Compound BCOR + MYLK burden	Surgical risk stratification / MPV
39438869	Czech OFCD families dental phenotype	Radiculomegaly 3/5; novel frameshift variants
30544426	Radiological findings & radiculomegaly	+14.8 SD root length; 30-yr follow-up
20825507	Endodontic treatment of radiculomegaly	47.5 mm root; treatment challenge

Limitations and Knowledge Gaps

1. **Epidemiology:** No reliable prevalence/incidence estimates; case-report-driven knowledge with ascertainment bias.
2. **Quality-of-life:** No formal EQ-5D/SF-36/PROMIS data.
3. **Tumor risk:** The neoplasia association (lymphoma, insulinoma) is based on single/few cases; magnitude of risk and surveillance guidelines are undefined.
4. **Genotype–phenotype:** Beyond the null-vs-P85L rule, fine correlations (variant position, X-inactivation quantification) remain incompletely mapped.
5. **Therapeutics:** No disease-modifying therapy, no clinical trials; the reversibility of chromatin derepression is untested clinically.
6. **Animal models:** No naturally occurring veterinary counterpart; no model reproduces the full human tetrad.

Proposed Follow-up Experiments / Actions

1. **Establish an international OFCD registry** to define prevalence, natural history, and tumor incidence with standardized QoL instruments.
2. **Quantitative X-inactivation studies** correlating skewing with expressivity to enable prognostic counseling.
3. **Tumor-surveillance protocol development** given emerging lymphoma/insulinoma reports — assess whether periodic endocrine/hematologic screening is warranted.
4. **Patient-derived iPSC/organoid models** (dental, cardiac, retinal) to test whether pharmacologic modulation of Notch, HDAC (e.g., HDAC inhibitors), or NMD can rescue OFCD-relevant transcriptional programs.
5. **Chromatin profiling (CUT&RUN/ChIP-seq for H2Aub, H3K4/H3K36me) in patient cells** to build a tissue-specific derepression map and identify additional therapeutic targets.
6. **Systematic ACMG-based reclassification** of all reported *BCOR* variants and functional assays for rare missense variants to sharpen genotype–phenotype boundaries between OFCD and Lenz.

Report compiled from 7 confirmed findings and 26 reviewed publications. Evidence source types: predominantly human clinical case reports/series, mouse and Xenopus model organism studies, and in vitro patient-cell mechanistic work.
