Blepharocheilodontic Syndrome 2 (CTNND1): Comprehensive Disease Characterization

Causal gene: CTNND1 (δ1-catenin / p120-catenin / p120ctn), HGNC:2515, Ensembl ENSG00000198561, chromosome 11q12.1. **Disease identifiers:** MONDO:0040503 · OMIM:617681 · DOID:0080346 · MedGen:1623594 · UMLS:C4540127 · Orphanet ORPHA:1997 (Blepharo-cheilo-dontic syndrome, gene-agnostic parent entity).

Blepharocheilodontic syndrome 2 (BCDS2) is the **CTNND1-related** form of blepharo-cheilo-dontic (BCD) syndrome. It must not be confused with BCDS1 (OMIM 119580), the allied disorder caused by *CDH1* (E-cadherin) — both genes encode members of the same epithelial cadherin–catenin adhesion complex, and the clinical phenotypes overlap, but the causal gene for the disease requested here (MONDO:0040503 / OMIM 617681) is **CTNND1**.

> Evidence sourcing note: BCDS2 is an ultra-rare Mendelian disorder. The information below is derived from **aggregated disease-level resources** (OMIM, Monarch/HPO, Orphanet, gnomAD) and from **primary individual-patient case series / cohort reports** (human clinical) plus **model-organism (mouse, Xenopus, zebrafish) and in-vitro** functional studies. There are no large EHR cohorts or omics datasets specific to BCDS2.

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1. Disease Information

BCDS2 is a rare autosomal dominant congenital malformation syndrome affecting the **eyelids (blepharo-), lip/palate (cheilo-), and teeth (-dontic)**. The classic triad comprises eyelid malformations (lagophthalmos, ectropion of the lower eyelids, euryblepharon, distichiasis), cleft lip and/or palate, and ectodermal/dental anomalies (oligodontia, conical teeth). The CTNND1-related form additionally carries an expanded spectrum including congenital heart defects, limb anomalies, neurodevelopmental problems, and more recently reported genitourinary and CNS anomalies

(P 32196547 ; P 40028877). P 39487033

- **Key identifiers:** MONDO:0040503; OMIM 617681; Orphanet ORPHA:1997 (BCD syndrome); DOID:0080346; MedGen C1623594/CUI 1623594; UMLS C4540127. ICD-10: Q87.0 (congenital malformation syndromes predominantly affecting facial appearance); ICD-11: LD2F.1Y/ nearest "other specified syndromes with facial/structural anomalies." No dedicated MeSH descriptor exists; indexed under cleft lip/palate and eyelid abnormality terms.
- **Synonyms:** Blepharocheilodontic syndrome type 2; blepharo-cheilo-odontic syndrome caused by mutation in CTNND1; CTNND1 blepharo-cheilo-odontic syndrome; BCDS2; BCD syndrome (CTNND1-related). Historically overlaps with "lagophthalmos–cleft lip/palate" descriptions (P 15930907).
- **Monarch definition:** "Any blepharo-cheilo-odontic syndrome in which the cause of the disease is a mutation in the CTNND1 gene."

2. Etiology

Primary cause — genetic. BCDS2 is caused by **heterozygous loss-of-function (protein-truncating) variants in CTNND1**, acting through haploinsufficiency (P 28301459 ; P 29348693). P 32196547
It is a monogenic, autosomal dominant disorder; there is no infectious or primarily environmental etiology.

- **Genetic risk factors:** The causal variant itself is the risk factor. Most BCDS2 variants are *de novo* (6/8 in Alharatani 2020, P 32196547), but transmitted (inherited) variants occur in multigenerational families (e.g., a four-

generation Chinese pedigree with c.83delG p.(Ala29Argfs*55*),

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P *36584998*

*A positive family history** raises recurrence risk to ~50% per the dominant pattern.

- **Environmental / lifestyle / occupational risk factors:** None established specific to BCDS2. General orofacial-cleft risk modifiers (maternal smoking, folate status, teratogens) are not demonstrated to modulate this monogenic syndrome.
- **Protective factors:** None identified (no protective alleles or environmental factors reported). The extreme population depletion of CTNND1 LoF variants (gnomAD) reflects purifying selection, not a protective mechanism.
- **Gene–environment interactions:** Not documented for BCDS2. Variable expressivity (below) is presumed to reflect genetic background/modifiers and stochastic developmental factors rather than defined exposures.
- **Modifier genes:** Not formally established. Mechanistically plausible modifiers are other components of the cadherin–p120 complex (CDH1, CDH3/P-cadherin, PLEKHA7, PLEKHA5, ESRP2); the 2026 mouse work shows combined E-/P-cadherin dosage sets a fusion threshold ( ), P 41231213 implying cadherin-pathway dosage could modulate severity.

3. Phenotypes (with HPO terms and HPOA frequencies)

Curated HPO annotations (Monarch/HPOA) and cohort reports give the following. Onset is **congenital** for all structural features; course is **stable/non-progressive** (a congenital malformation syndrome), though secondary problems (corneal exposure, malocclusion) can worsen without treatment.

Phenotype	HPO term	Frequency	Type
Conical tooth	HP:0000698	~100%	physical/dental sign
Tooth agenesis / oligodontia	HP:0009804 (HP:0000156)	~100% (mean 13.7 missing permanent teeth, range 7–17; P 28181393)	physical/dental
Ectropion of lower eyelids	HP:0007651	~100%	clinical sign
Cleft lip (± palate)	HP:0410030 / HP:0000175	~67% (bilateral common)	physical
Distichiasis	HP:0009743	~67%	clinical sign
Euryblepharon	HP:0012905	~67%	clinical sign
Lagophthalmos	HP:0030001	~67%	clinical sign
Cutaneous syndactyly	HP:0012725	occasional	physical
Facial asymmetry	HP:0000324	occasional	physical
Nail dysplasia	HP:0002164	reported	ectodermal
Flat face / high forehead / hypertelorism	HP:0012368 / HP:0000348 / HP:0000316	reported	craniofacial
Class III malocclusion, short/ narrow maxilla, taurodontism	HP:0000689 (taurodontism)	cohort: all patients (P 28181393)	dental/skeletal
Congenital heart defect	HP:0001627	subset (P 32196547)	structural
Limb anomalies	HP:0002813	subset (P 32196547)	structural
	HP:0001263 / HP:0012758		neurobehavioral

Phenotype	HPO term	Frequency	Type
Developmental delay / neurodevelopmental disorder		subset (P 32196547)	
Genitourinary anomalies (duplex kidney, ureterocele, bicornuate uterus)	HP:0000107/ HP:0000070/ HP:0000813	rare (P 40028877)	structural
Hydrocephalus (prenatal)	HP:0000238	rare (P 39487033)	CNS

- **Severity:** Variable; dental and lower-eyelid signs essentially fully penetrant, clefting and classic eyelid features highly frequent (~67%).
- **Quality-of-life impact:** Feeding and speech difficulties (cleft), ocular-surface discomfort and keratopathy risk (lagophthalmos/ectropion/distichiasis), dental function and facial aesthetics (oligodontia, malocclusion), and psychosocial impact. No disease-specific EQ-5D/SF-36 data exist; QoL inferred from general cleft and oligodontia literature.

4. Genetic / Molecular Information

- **Causal gene:** CTNND1 (HGNC:2515; OMIM *601045), encoding p120-catenin/δ1-catenin; UniProt O60716. Protein domains: N-terminal coiled-coil/regulatory domain and central Armadillo (ARM) repeat domain that binds the cadherin juxtamembrane domain.
- **Variant types:** Predominantly **protein-truncating** — frameshift (e.g., c.83delG p.Ala29Argfs*55*, P *36584998*), *nonsense, and canonical splice-site** variants (e.g., de novo splice variant, P 40028877). Ghoumid 2017 described 3 truncating CTNND1 variants; Kievit 2018 added more; Alharatani 2020 reported 8 novel truncating variants (6 de novo) (P 28301459 ; 29348693; 32196547). Some rare missense variants are reported in the broader CTNND1-cleft spectrum.

- **ACMG/AMP classification:** Truncating variants in this LoF-intolerant gene typically meet pathogenic/likely-pathogenic criteria (PVS1 + de novo PS2/PM6 + absence in gnomAD PM2).
- **Allele frequency:** Pathogenic alleles are absent/ultra-rare in gnomAD. Gene-level constraint (gnomAD): **pLI = 1.00, LOEUF = 0.217, observed/expected LoF = 0.143 (16 observed vs 112 expected), LoF Z = 7.70; missense Z = 3.00** — among the most LoF-intolerant genes in the genome, strongly supporting haploinsufficiency.
- **Somatic vs germline:** Germline (constitutional); de novo or inherited. (Somatic CTNND1/CDH1-pathway alterations occur in cancers but are unrelated to this congenital syndrome.)
- **Functional consequence: Loss of function / haploinsufficiency** (reduced p120-catenin dosage destabilizing surface cadherins). Dominant-negative mechanisms characterize *CDH1* BCDS1 variants, not CTNND1 LoF.
- **Modifier genes:** See §2. **Epigenetics:** No disease-specific methylation/histone signature reported. **Chromosomal abnormalities:** BCDS2 is a single-gene disorder; no recurrent cytogenetic rearrangement — though a contiguous 17q12 microdeletion was an incidental, unrelated finding in one family
(P 36584998).

5. Environmental Information

Not applicable as a primary driver. **Environmental factors, lifestyle factors, and infectious agents are not causative** of BCDS2; it is a monogenic developmental disorder. General teratogen avoidance in pregnancy is prudent but does not specifically prevent or modify this genetic condition.

6. Mechanism / Pathophysiology

Ordered causal chain (initiating lesion → clinical manifestation):

1. A heterozygous truncating/splice CTNND1 variant **leads to** nonsense-mediated decay / a non-functional allele → **reduced p120-catenin (δ1-catenin) dosage (haploinsufficiency)** [demonstrated: gnomAD constraint, clinical LoF variants].
2. Reduced p120-catenin **results in** failure to cap and stabilize the cadherin cytoplasmic juxtamembrane domain → **increased cadherin (E-cadherin/CDH1, P-cadherin/CDH3) endocytosis and turnover**, lowering surface cadherin levels [demonstrated in vitro/mouse:

P 28301459 ’

P 41231213].

3. Lowered cadherin levels **drop adhesion below the elevated threshold specifically required for upper-lip epithelial fusion**, and dysregulate **actomyosin contractility** needed to drive fusion → **failed epithelial tissue fusion/integrity** [demonstrated, mouse live-imaging + allelic series:

P 41231213].

4. Failed fusion/epithelial integrity in the developing **lip, palate, eyelid margins, and tooth-forming (dental lamina) epithelia → cleft lip/palate, eyelid malformations (lagophthalmos, ectropion, euryblepharon, distichiasis), and tooth agenesis/conical teeth** [demonstrated: conditional Cdh1/Ctnnd1 mouse deletions recapitulate BCD-like eyelid, craniofacial, tooth features; Ctnnd1-KO recapitulates CL/P:

P 28301459 ’

P 29805042].

5. **Branch A (adhesion/contractility):** the principal, developmentally essential route — p120's **cadherin-stabilizing** function; its RhoA- and Kaiso-binding functions are **dispensable** in mammalian development

(P 41231213).

6. **Branch B (Wnt/transcriptional):** reduced p120 also **lowers protection of β-catenin from GSK3β-ubiquitin–mediated degradation**, attenuating **Wnt/β-catenin signaling** and perturbing EMT/transcription (Kaiso de-repression) — inferred contributor to vascular/ other phenotypes; GSK3β inhibition (LiCl, CHIR-99021) rescues in the CTNND1-FEVR model

(P 35700046).

7. Additional **p120 roles in neural-crest–derived periocular mesenchyme** → anterior-segment/ocular contributions (Wnt1-Cre Ctnnd1 ablation causes anterior segment dysgenesis in mice:

P 22736606)

— mechanistic support for the ocular component.

8. **Molecular pathways:** Adherens junction (KEGG hsa04520), Wnt signaling (hsa04310), Rho GTPase/actomyosin contractility, Rap1 signaling. **Reactome:** adherens junctions interactions; degradation/stabilization of β-catenin.
9. **Cellular processes:** Cell–cell adhesion, epithelial tissue fusion, epithelial–mesenchymal transition (EMT), cell migration, regulation of actomyosin contractility, cadherin recycling/endocytosis.
10. **Protein dysfunction:** Quantitative **loss of function** (reduced protein), not aggregation/misfolding; downstream loss of cadherin stabilization.
11. **Metabolic / immune / oxidative:** No primary metabolic, autoimmune, or oxidative-stress mechanism; tissue "damage" is **developmental dysmorphogenesis** (failed fusion), not degeneration.
12. **GO terms:** GO:0016339 (calcium-dependent cell–cell adhesion via plasma-membrane adhesion molecules), GO:0045216 (cell–cell junction organization), GO:0016055 (Wnt signaling pathway), GO:0001837 (epithelial to mesenchymal transition), GO:0003382 (epithelial cell morphogenesis), GO:0060662 (salivary/epithelial fusion-related morphogenesis), GO:0097178 (ruffle assembly/actomyosin). **Cellular component:** GO:0005913 (cell–cell adherens junction), GO:0005912 (adherens junction), GO:0016342 (catenin complex).
13. **Cell types (CL):** epithelial cell (CL:0000066), keratinocyte (CL:0000312), neural crest cell (CL:0000333), cranial neural crest–derived mesenchyme, odontogenic/dental epithelial cells, endothelial cell (CL:0000115, relevant to the FEVR/vascular branch).
14. **Molecular profiling:** No BCDS2-specific transcriptomic/proteomic/metabolomic dataset. Model work used proteomics to define the p120–β-catenin–Wnt axis (P 35700046) and functional CRISPR/Cas9 Xenopus and conditional-mouse approaches (P 32196547).

7. Anatomical Structures Affected

- **Primary organs/structures:** Eyelids (UBERON:0000074) and eyelid margin; upper/lower lip (UBERON:0001833) and lip fusion sites; secondary palate/palatal shelves (UBERON:0001716); teeth and dental lamina (UBERON:0001091); skin/hair/nails (ectodermal derivatives).

- **Secondary / associated involvement:** Heart (UBERON:0000948) — congenital cardiac anomalies; limbs (UBERON:0002101); kidney/urinary tract (UBERON:0000057/0002113) and uterus (UBERON:0000995) in rare cases; brain/ventricular system (UBERON:0000955) — rare hydrocephalus; anterior segment of eye (cornea/iris) via neural-crest mechanism (model data).
- **Body systems:** Integumentary/craniofacial, ocular/visual, digestive (oral), cardiovascular, musculoskeletal (limb/skeletal malocclusion), and in a minority CNS and genitourinary.
- **Tissue/cell level:** Primarily **epithelial tissue** (and its adherens junctions) plus **neural-crest–derived craniofacial mesenchyme**. **Subcellular (GO CC):** plasma membrane / cell–cell adherens junction (GO:0005913), catenin complex (GO:0016342), cytoplasm.
- **Lateralization:** Eyelid and clefting features are typically **bilateral** (bilateral cleft lip/palate is characteristic; P 28181393), though unilateral clefts occur (P 40028877); facial asymmetry may be present.

8. Temporal Development

- **Onset: Congenital** — structural anomalies form during embryonic craniofacial morphogenesis; some are detectable **prenatally** (P 39487033).
- **Onset pattern:** Non-acute, developmental/insidious (present at birth).
- **Progression: Stable/non-progressive** malformations; disease duration is **lifelong**. Secondary deterioration (exposure keratopathy, malocclusion, dental loss, speech/feeding difficulty) can progress if untreated but the primary lesions do not advance.
- **Critical period / window of opportunity:** The developmental critical period is **embryonic facial fusion** (weeks ~4–10 of human gestation); therapeutically, the actionable windows are **postnatal surgical/reconstructive** (cleft repair in infancy, eyelid surgery to protect the cornea, dental rehabilitation in childhood/adolescence). No remission/relapse pattern (not applicable to a congenital malformation).

9. Inheritance and Population

- **Inheritance: Autosomal dominant** (P 29348693).
  Both de novo and transmitted; recurrence risk ~50% for an affected parent; de novo cases carry low recurrence risk tempered by possible **gonadal mosaicism** (reported for the broader group; specific CTNND1 mosaicism data limited).
- **Penetrance:** High/essentially complete for the dental/eyelid signs; **expressivity is variable** (intra- and interfamilial). Classic clefting features are incompletely penetrant (~67%).
- **Anticipation:** Not applicable (not a repeat-expansion disorder).
- **Founder effects / consanguinity:** None established; a dominant disorder, consanguinity is not a driver.
- **Carrier frequency / population:** No carrier state (dominant); pathogenic alleles are ultra-rare/absent in gnomAD.
- **Epidemiology: Ultra-rare.** Orphanet prevalence for BCD syndrome is **<1/1,000,000**; only a few dozen patients across both CDH1 and CTNND1 forms are reported in the literature. No reliable incidence figure. No strong ethnic predilection (cases reported from Europe, Asia, the Americas, India, the Middle East). **Sex ratio:** no clear sex bias (reported in both sexes). **Age distribution:** diagnosed at birth/infancy.

10. Diagnostics

- **Clinical recognition:** Diagnosis is suspected on the **characteristic triad** (eyelid malformations + cleft lip/palate + oligodontia/conical teeth) and confirmed by **molecular genetic testing** of CTNND1 (and CDH1 for BCDS1).
- **Genetic testing (recommended approach): Gene-panel or exome/genome sequencing** is the mainstay; targeted single-gene/Sanger of CTNND1 can confirm a familial variant. CTNND1 is included on cleft-palate, orofacial-cleft, and craniofacial/eyelid-anomaly NGS panels. WES/WGS with **reverse phenotyping** enabled a prenatal diagnosis (P 39487033).
  Chromosomal microarray is not diagnostic for this single-gene disorder but may be used to exclude CNV mimics (e.g., 22q11.2 deletion given velocardiofacial overlap).

- **Imaging / functional / other tests:** Not diagnostic per se but used to delineate complications — **echocardiography** (cardiac anomalies), **renal/pelvic ultrasound** (genitourinary anomalies; recommended at diagnosis per P 40028877), cephalometric/dental radiographs (malocclusion, oligodontia; P 28181393), ophthalmologic exam (corneal exposure). No specific biochemical biomarker, enzyme assay, histopathology finding, or liquid-biopsy test exists.
- **Clinical criteria / differential diagnosis:** No formal consensus criteria. **Differential diagnosis:** BCDS1 (CDH1); ankyloblepharon–ectodermal defects–cleft lip/palate (AEC/Hay–Wells, TP63); ectrodactyly–ectodermal dysplasia–clefting (EEC, TP63); van der Woude syndrome (IRF6, lip pits); velocardiofacial/22q11.2 deletion syndrome; Kabuki syndrome; isolated non-syndromic cleft lip/palate; and isolated lagophthalmos/euryblepharon (P 15930907). Distinguishing features: BCD's combination of distichiasis/euryblepharon/ectropion with oligodontia and clefting, plus a CTNND1 (or CDH1) variant.
- **Screening:** No population newborn screening (ultra-rare). **Cascade genetic testing** of at-risk relatives and **prenatal/preimplantation testing** are available once a familial variant is known.

11. Outcome / Prognosis

- **Survival / life expectancy:** Generally **normal life expectancy** for patients without severe cardiac or CNS involvement; BCDS2 is not intrinsically life-limiting. No disease-specific mortality statistics; deaths would relate to major associated anomalies (complex congenital heart disease, severe CNS malformation) in a minority.
- **Morbidity / disability:** Mostly **functional and reconstructive** — ocular-surface disease from lagophthalmos/ectropion/distichiasis (risk of corneal exposure keratopathy and visual impairment if untreated), feeding and speech impairment from clefting, dental dysfunction and facial/aesthetic concerns from oligodontia and Class III malocclusion, and possible developmental/learning difficulties in the subset with neurodevelopmental involvement.

- **Disease course:** Stable primary lesions; outcomes are generally **good with multidisciplinary treatment**. **Complications:** exposure keratopathy, recurrent otitis media/hearing issues (cleft palate), speech/velopharyngeal dysfunction, malocclusion.
- **Prognostic factors:** Presence and severity of cardiac, CNS, and neurodevelopmental involvement are the main determinants of overall prognosis; isolated craniofacial involvement has an excellent prognosis. No molecular prognostic biomarker; genotype–phenotype correlation is weak given small numbers (CDH1 variants may be more severe than CTNND1 per

(P 28301459).

12. Treatment

No disease-modifying, pharmacologic, gene, cell, or RNA therapy exists. Management is **symptomatic, surgical, and multidisciplinary** (P 20073547).

- **Surgical / interventional:** Cleft lip repair (NCIT: Cleft Lip Repair) and cleft palate repair (Cleft Palate Repair) in infancy by a cleft team; **oculoplastic/ophthalmic surgery** for lagophthalmos, ectropion, euryblepharon, and distichiasis to protect the cornea; orthognathic surgery for Class III malocclusion.
- **Dental / prosthodontic:** Rehabilitation of oligodontia with **overdentures**, dental implants, orthodontics, and restorative care (P 20073547); NCIT: Dental Prosthesis, Dental Implant, Orthodontic Therapy.
- **Supportive / rehabilitative:** Ocular lubricants/moisture protection for exposure; **speech therapy** (NCIT: Speech Therapy); feeding support in infancy; audiology and ENT care; developmental/educational support where needed.
- **Pharmacotherapy / pharmacogenomics:** None specific. **Advanced/targeted therapeutics, immunotherapy, gene/cell/RNA therapy:** none approved or in trials for BCDS2 (no registered ClinicalTrials.gov interventional trials specific to this ultra-rare disorder). The GSK3β-inhibitor rescue of the CTNND1/Wnt axis (LiCl, CHIR-99021) is **experimental, cell/animal-level only** and specific to the FEVR context

(P 35700046), not a human BCDS2 therapy.

- **Treatment strategy:** Coordinated craniofacial-team pathway (ophthalmology, plastic/oral-maxillofacial surgery, dentistry/orthodontics, speech-language pathology, cardiology, nephrology, clinical genetics) with staged interventions across childhood.
- **NCIT intervention concepts:** Cleft Lip Repair; Cleft Palate Repair; Oculoplastic Surgery; Dental Prosthesis/Overdenture; Dental Implant; Orthognathic Surgery; Speech Therapy; Genetic Counseling.

13. Prevention

- **Primary prevention:** Not possible for the genetic lesion. **Genetic counseling** (NCIT: Genetic Counseling) for recurrence-risk assessment (~50% for an affected parent) is central.
- **Secondary prevention / early detection: Prenatal diagnosis** (ultrasound + molecular testing with reverse phenotyping; P 39487033) and **preimplantation genetic testing (PGT-M)** where a familial variant is known; **cascade testing** of relatives. Early postnatal multidisciplinary evaluation (cardiac echo, renal ultrasound, ophthalmologic exam) for timely intervention.
- **Tertiary prevention:** Protecting the cornea (prevent exposure keratopathy), timely cleft/palate repair (speech/feeding), dental and orthodontic care, and surveillance of associated organ systems to prevent complications.
- **Immunization / public-health / environmental measures:** Not applicable (non-infectious, non-environmental).

14. Other Species / Natural Disease

- **Taxonomy / orthologs:** Human CTNND1 (NCBI Gene 1500). Orthologs: mouse *Ctnnd1* (NCBI Gene 12388, MGI:105100), zebrafish *ctnnd1* (NCBI Gene 556726), *Xenopus* ctnnd1. p120-catenin is **highly evolutionarily conserved** across vertebrates, and the cadherin–catenin adhesion mechanism is deeply conserved.
- **Natural/veterinary disease:** No naturally occurring CTNND1 blepharocheilodontic syndrome is catalogued in companion animals or wildlife (not listed in OMIA as a

spontaneous CTNND1 disorder). Disease knowledge derives from **engineered** models rather than natural animal disease.

- **Comparative biology:** Conditional/engineered loss of Cdh1/Ctnnd1 in mice reproduces eyelid, craniofacial, and tooth phenotypes reminiscent of human BCD (P 28301459), indicating conserved mechanism. **Zoonotic potential:** none (not an infectious disease).

15. Model Organisms

- **Mouse (Mus musculus, NCBI Taxon 10090):** The principal model. **Conditional knockouts** of *Ctnnd1* (and *Cdh1*) in relevant lineages recapitulate BCD-like eyelid, craniofacial, and tooth defects (P 28301459); **Ctnnd1 knockout mice recapitulate the cleft lip/palate spectrum** (P 29805042); **Wnt1-Cre; Ctnnd1^fl/fl** neural-crest ablation causes ocular anterior-segment dysgenesis (P 22736606). A 2026 **allelic series** separated p120 functions, showing cadherin stabilization is essential while RhoA/Kaiso binding is dispensable, and defined a cadherin adhesion threshold for lip fusion (P 41231213). Model type: mammalian, genetic (knockout/conditional/knock-in allelic series).
- **Xenopus: CRISPR/Cas9 targeting of ctnnd1** reproduced a subset of craniofacial/epithelial phenotypes and revealed additional mesenchymal roles (P 32196547).
- **Zebrafish (Danio rerio, NCBI Taxon 7955):** Functional assays of cadherin–catenin complex variants (used for CDH1 BCDS variants) support dominant impairment of adhesion (P 29348693).
- **In-vitro / cellular:** Human epithelial and endothelial cell lines and trabecular-meshwork cells used to show cadherin/β-catenin membrane loss and Wnt-axis effects

(; P 22736606). P 35700046

- **Phenotype recapitulation & limitations:** Models reproduce clefting, eyelid/ocular, and tooth phenotypes well, validating the adhesion-threshold mechanism; limitations include incomplete modeling of the full human multisystem spectrum (e.g., human neurodevelopmental/genitourinary features) and species differences in facial morphogenesis. Resources: MGI, IMPC, ZFIN, Xenbase, Alliance of Genome Resources.

Summary of Supported vs. Refuted Hypotheses

Supported (evidence-backed): - BCDS2 is caused by heterozygous CTNND1 loss-of-function/truncating variants via haploinsufficiency (human cohorts + gnomAD constraint pLI=1.0, LOEUF=0.22). - The core mechanism is destabilization of surface cadherins and failure of an actomyosin-dependent cadherin adhesion threshold required for craniofacial epithelial fusion (mouse allelic series,). P 41231213

- A secondary Wnt/β-catenin branch (p120 protects β-catenin from GSK3β-mediated degradation) contributes to CTNND1-related phenotypes ( ). P 35700046

- Dental and lower-eyelid features are near-fully penetrant; clefting ~67%; expression is variable (HPOA).

Refuted / downgraded: - p120's RhoA- and Kaiso-binding (transcriptional repressor) functions are **not** the essential developmental mechanism — they are dispensable in vivo, with cadherin stabilization being crucial ( ). P 41231213

- A dominant-negative mechanism is **not** the model for CTNND1 (that applies to CDH1/BCDS1); CTNND1 acts by LoF/haploinsufficiency.

Limitations and Future Directions

- Ultra-rare disease: small cohorts preclude robust genotype–phenotype correlation and precise frequency estimates; many "frequencies" derive from HPOA annotations on limited cases.
- No BCDS2-specific omics (transcriptomic/proteomic/metabolomic) or QoL datasets exist.
- The full extent of the expanding phenotype (cardiac, CNS, genitourinary, neurodevelopmental) needs prospective natural-history study.
- Mechanistic translation (e.g., whether modulating cadherin dosage or Wnt signaling could ever be preventive) remains experimental.

Evidence types are indicated inline: human clinical (case series/cohorts), model organism (mouse/Xenopus/zebrafish), in vitro (cell lines), and computational (gnomAD constraint, ontology curation).
