3MC Syndrome — Comprehensive Disease Characterization Report

Prepared for a disease knowledge base entry. Evidence type is human clinical unless otherwise noted (model organism / in vitro / computational). Primary literature cited by PMID.

Summary (Answer to the Research Question)

3MC syndrome is a rare, autosomal-recessive congenital malformation syndrome that unifies four historically separate disorders — **M**alpuech, **M**ichels, **M**ingarelli and **C**arnevale syndromes ("3MC"). It is caused by biallelic loss-of-function variants in one of three genes of the **lectin pathway of complement**: **MASP1** (encoding MASP-1/MASP-3), **COLEC11** (encoding collectin-11/CL-K1), and **COLEC10** (encoding collectin-10/CL-L1). The shared mechanism is loss of a collectin/MASP-3 chemoattractant guidance cue required for **neural crest cell migration**, producing a distinctive facial gestalt (hypertelorism, blepharophimosis, blepharoptosis, highly arched eyebrows) together with cleft lip/palate, postnatal growth deficiency, developmental delay, hearing loss, a characteristic caudal appendage, skeletal (craniosynostosis, radioulnar synostosis) and genitourinary anomalies (PMIDs 21258343, 28301481).

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1. Disease Information

- **Overview:** A rare autosomal-recessive multiple-congenital-anomaly / dysmorphism syndrome affecting craniofacial, skeletal, genitourinary, ophthalmic and (variably) cardiac development. The name "3MC" was proposed as a unifying term for the overlapping Carnevale, Mingarelli, Malpuech and Michels syndromes
  (P 21258343).
- **Key identifiers (suggested):**
- **MONDO:** MONDO:0018721 ("3MC syndrome") — with subtypes 3MC syndrome type 1/2/3.

- **OMIM (phenotype):** 3MC syndrome 1 (**#257920**, *MASP1/COLEC11* — historically Malpuech/Carnevale), 3MC syndrome 2 (**#265050**, *COLEC11*), 3MC syndrome 3 (**#248340**, *COLEC10* — historically Michels). (PMIDs 36503917, 34636477)
- **OMIM (gene):** MASP1 *600521; COLEC11* 612502; COLEC10 *607620.
- **Orphanet:** ORPHA:293843 (3MC syndrome); legacy entries Malpuech syndrome (ORPHA:1993), Michels syndrome (ORPHA:1394), Carnevale/Mingarelli.
- **ICD-10:** Q87.0 (congenital malformation syndromes predominantly affecting facial appearance). **ICD-11:** LD2F.0Y (other specified syndromes with facial features as a major feature).
- **MeSH:** No dedicated descriptor; indexed under "Abnormalities, Multiple" / supplementary concept "3MC syndrome."
- **Synonyms / alternative names:** Malpuech–Michels–Mingarelli–Carnevale syndrome; Malpuech facial clefting syndrome; Michels syndrome; Carnevale syndrome; Mingarelli syndrome; Malpuech syndrome; OSA syndrome; craniofacial-ulnar-renal syndrome; blepharophimosis-ptosis-cleft-lip syndrome (descriptive).
- **Data derivation:** Information here is derived from **aggregated disease-level resources** (OMIM/Orphanet) and **individual patient case reports / small cohorts** (fewer than ~100 molecularly confirmed patients worldwide). There is no large EHR-based dataset for this ultra-rare disorder.

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2. Etiology

- **Primary cause — genetic:** Biallelic (homozygous or compound heterozygous) pathogenic variants in **MASP1**, **COLEC11**, or **COLEC10** — all encoding components of the lectin complement pathway
(
P 21258343
:
"identified two mutated genes, COLEC11 and MASP1, both of which encode proteins in the lectin complement pathway";

P 28301481
for COLEC10). There is evidence of further **genetic heterogeneity**: some clinically typical

patients from consanguineous families have no MASP1/COLEC11/COLEC10 variant (P 26789649).

- **Genetic risk factors:**
- Causal variants in the three genes (Section 4).
- **Consanguinity** — a major risk factor; most reported families are consanguineous with homozygous variants.
- **Founder alleles** — e.g., COLEC10 c.311G>T (p.Gly104Val) in Ashkenazi Jews (carrier frequency ~1/99; P 35943032); COLEC10 c.807_810delCTGT in Apulia, Italy (P 34740859).
- **Modifier genes:** Model-organism data suggest other complement components (MASP-2, factor B, C3) may modify skeletal severity (P 41774788 , model organism).
- **Environmental risk factors:** None established. 3MC is a monogenic Mendelian disorder; no toxin, infectious, lifestyle, occupational, age or sex exposure is a known cause. (Not applicable.)
- **Protective factors:** No genetic or environmental protective factors described for the developmental syndrome. (Free **L-fucose** is protective against CL-11-mediated *renal ischemia-reperfusion injury* in mice — P 31914693 — but this concerns adult acquired injury, not the developmental syndrome.)
- **Gene–environment interactions:** None documented for 3MC syndrome. (Not applicable.)

3. Phenotypes

Frequencies drawn largely from a 7-patient cohort (

P *41703727*

) and case series (PMIDs 36503917, 26789649). Onset is congenital/prenatal for structural features; course is generally stable/non-progressive (malformative) with lifelong sequelae.

Phenotype	Type	HPO term	Frequency / notes
Hypertelorism	physical/ craniofacial sign	HP:0000316	Very frequent; core gestalt
Blepharophimosis	physical sign	HP:0000581	Frequent; core gestalt
Blepharoptosis (ptosis)	physical sign	HP:0000508	7/7 in cohort; core gestalt
Highly arched eyebrows	physical sign	HP:0002553	7/7; core gestalt
Epicanthus inversus	physical sign	HP:0000537	Frequent
Downslanted palpebral fissures	physical sign	HP:0000494	Frequent
Cleft lip and/or palate (often bilateral)	physical malformation	HP:0000202 / HP:0000175	~6/7 (86%); variable — may be absent
Postnatal growth deficiency / short stature	clinical sign	HP:0008897 / HP:0004322	Frequent
Global developmental delay / intellectual disability	behavioral/ cognitive	HP:0001263 / HP:0001249	Common (7/7 neuromotor delay in cohort); variable severity, may be absent
Hearing loss	lab/functional sign	HP:0000365	~4/7 (57%)
Caudal appendage / prominent elongated coccyx (sacral protuberance)	physical sign	HP:0100541 (tail-like) / sacral appendage	~4/7; relatively specific diagnostic clue
Craniosynostosis	physical sign	HP:0001363	Subset
Radioulnar synostosis	physical sign	HP:0003042	Subset; limb feature
Genital anomalies (e.g., hypospadias, cryptorchidism)	physical sign	HP:0000078 / HP:0000047 / HP:0000028	Subset
	physical sign	HP:0000119 / HP:0000085	Subset

Phenotype	Type	HPO term	Frequency / notes
Vesicorenal anomalies (horseshoe/pelvic kidney, reflux)			
Congenital heart disease (e.g., PDA)	physical sign	HP:0001627 / HP:0001643	~2/7 (29%)
Anterior chamber / anterior-segment dysgenesis	ophthalmic sign	HP:0007700	Subset (notably Michels-type)
Umbilical / periumbilical anomalies, umbilical hernia	physical sign	HP:0001537	~6/7 in recent cohort
Clinodactyly of 5th finger	physical sign	HP:0004209	Subset
High myopia	ophthalmic sign	HP:0011003	Reported
Behavioral/psychiatric (ADHD, ODD, depression)	behavioral	HP:0007018 / —	Case-reported comorbidity (P 37463393)

- **Age of onset:** Congenital/prenatal (structural malformations detectable prenatally — bilateral cleft lip/palate + sacral protuberance + renal anomaly; P 32441374). Growth deficiency is *postnatal*.
- **Severity:** Variable (mild to severe), even within the same gene and family (P 29407414 describes an adult with the facial gestalt but without cleft lip/palate, intellectual disability, or short stature).
- **Progression:** Non-progressive/stable malformative disorder; sequelae are lifelong.
- **Quality-of-life impact:** Cleft repair, hearing loss, developmental delay, short stature and limb/skeletal anomalies affect feeding, speech, hearing, mobility and learning; no formal EQ-5D/SF-36 studies exist for this ultra-rare disease (not available).

4. Genetic / Molecular Information

- **Causal genes (HGNC / locus / OMIM gene / product):**
- **MASP1** — HGNC:6901; 3q27.3; *600521; encodes MASP-1 and MASP-3 (alternative splicing). 3MC-causing variants are truncating, or missense within exon 12** encoding the MASP-3-specific C-terminal serine protease domain
(P 29407414).
- **COLEC11** — HGNC:17213; 2p25.3; *612502; encodes collectin-11 (CL-K1 / CL-11 / collectin kidney-1)*.*
- **COLEC10** — HGNC:2311; 8q24.12; *607620; encodes collectin-10 (CL-L1 / collectin liver-1)*.*
- **Representative pathogenic variants (all germline, biallelic):**
- COLEC11 p.Gly204Ser — associated with undetectable serum protein
(P 25912189 ,
in vitro).
- COLEC10 p.Arg9Ter (c.25C>T), p.Gly77Glufs*66 (c.226delA), p.Cys176Trp (c.528C>G) — impair CL-L1 expression/secretion
(P 28301481 ,
in vitro).
- COLEC10 c.311G>T; p.Gly104Val — Ashkenazi Jewish founder variant
(P 35943032).
- COLEC10 c.807_810delCTGT; p.Cys270Serfs*33 (loss of natural stop, +24 aa) — Apulian founder
(P 34740859).
- COLEC10 c.128_129delCA; p.Thr43AsnfsTer9 — Iranian, first homozygous frameshift
(P 34636477).
- MASP1 c.310C>T; p.Gln104Ter — nonsense
(P 33765348).
- MASP1 homozygous ~2 kb intragenic deletion partially affecting exon 12; also exon-level deletions (PMIDs 29407414, 41703727) — may be missed by standard exome pipelines.

- **Variant classification & type:** Pathogenic/likely pathogenic per ACMG/AMP; predominantly **loss-of-function** — nonsense, frameshift, splice, intragenic/exon-level deletions, and secretion-impairing missense. **Functional consequence** = **loss of function** (protein deficiency or non-secretion). No gain-of-function or dominant-negative mechanism reported.
- **Allele frequency:** Causal alleles are rare/absent in gnomAD except population-specific founders (Ashkenazi COLEC10 carrier freq ≈1.01%, P 35943032).
- **Somatic vs germline:** Exclusively **germline**, biallelic (autosomal recessive). No somatic/COSMIC relevance.
- **Modifier genes:** Complement components MASP-2, factor B, C3 modulate skeletal phenotype in mice (P 41774788, model organism).
- **Epigenetics:** No disease-specific methylation/histone signature reported (not available).
- **Chromosomal abnormalities:** None characteristic; the disorder is caused by single-gene point/indel/small-deletion variants (some detectable only by careful CNV analysis of WES/WGS; P 29407414).

Suggested gene/GO annotations: MASP1/COLEC11/COLEC10; GO:0001867 (complement activation, lectin pathway), GO:0030246 (carbohydrate binding), GO:0005509 (calcium ion binding).

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5. Environmental Information

- **Environmental factors:** None known. (Not applicable — Mendelian disorder.)
- **Lifestyle factors:** None known (not applicable).
- **Infectious agents:** None (not applicable). Note the biological irony that the causative genes are innate-immune anti-microbial pattern-recognition molecules, but the syndrome itself is developmental, not infectious.

6. Mechanism / Pathophysiology

Causal chain (upstream → downstream): Biallelic LOF variant in MASP1/COLEC11/COLEC10 → deficient or mis-secreted collectin (CL-K1 or CL-L1) or non-functional MASP-3 → loss of the **CL-K1·MASP-3 chemoattractant guidance cue** for **cranial neural crest cells (cNCC)** → aberrant NCC migration/differentiation → malformation of NCC-derived and midline structures (craniofacial skeleton, palate, heart outflow, genitourinary tract, vertebral/coccygeal elements) → clinical phenotype (P 21258343).

- **Molecular pathways:** Lectin pathway of complement (and its link to the alternative pathway). CL-K1/CL-L1 form Ca^{2+}-dependent heteromeric collectin complexes that associate with MASP-1/2/3 (P 27782323).
  MASP-3 is the exclusive pro-factor D activator in resting blood, linking the lectin and alternative pathways (P 27535802 : *"activated MASP-3 is the exclusive pro-FD activator in resting blood, which demonstrates a fundamental link between the lectin and alternative pathways."*).
- **Cellular processes: Neural crest cell migration** (GO:0001755) — CL-K1 acts as a directional guidance cue (P 21258343).
  Also **osteoclast differentiation** (GO:0030316) — CL-11 regulates osteoclastogenesis complement-dependently (P 41774788 , model organism/in vitro).
- **Protein dysfunction:** LOF via impaired **secretion** and loss of **Ca^{2+} binding** in the carbohydrate-recognition domain (CRD). Disease mutations do not necessarily block folding/oligomerization in vitro, but abolish Ca^{2+} binding and secretion, producing serum protein deficiency

(P 25912189 , in vitro).

- **Metabolic/biochemical:** CL-K1 recognizes **high-mannose oligosaccharides** and **L-fucose** on stressed/altered self-surfaces (PMIDs 25912189, 31914693). Enzymatically, MASP-3 has low amidolytic activity relative to other C1r/C1s/MASP proteases (P 23861840 , in vitro/structural).
- **Immune involvement:** The causative molecules are innate-immune complement effectors; however, 3MC patients are not primarily immunodeficient — the phenotype reflects the **developmental (non-immune) moonlighting role** of these proteins ("a broader functionality of the complement system than previously anticipated," P 27782323).
- **Tissue-damage mechanism (adult context):** In acquired renal ischemia-reperfusion injury, CL-11 binds a fucosylated damage ligand on tubular epithelium and triggers complement/C5b-9 injury — mechanistically informative but distinct from the developmental syndrome (PMIDs 28663231, 31914693, model organism).
- **Molecular profiling / omics / single-cell / CRISPR screens:** No disease-specific transcriptomic, proteomic, metabolomic or functional-genomics screens published for 3MC (not available); mechanistic evidence is from targeted zebrafish morphants, mouse expression/knockout, and in vitro biochemistry.

Suggested ontology terms: GO:0001755 (neural crest cell migration), GO:0001867 (lectin-pathway complement activation), GO:0030316 (osteoclast differentiation), GO:0045087 (innate immune response); **CL:0000333** (migratory neural crest cell / cranial NCC), CL:0000138 (chondrocyte), CL:0000092 (osteoclast); CHEBI:2181 (L-fucose), CHEBI:29108 (calcium(2+)), CHEBI:37671 (high-mannose oligosaccharide/mannose).

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7. Anatomical Structures Affected

- **Organ / system level:**
- **Craniofacial skeleton & face** (UBERON:0001456 face; UBERON:0001716 secondary palate) — cleft lip/palate, hypertelorism, dysmorphism.

- **Skull sutures** (UBERON:0000905) — craniosynostosis.
- **Eyes / periocular** (UBERON:0000970) — blepharophimosis, ptosis, anterior-segment dysgenesis (UBERON:0000481 anterior chamber).
- **Skeleton / limbs** — radioulnar synostosis (radius UBERON:0001423 / ulna UBERON:0001424); vertebral column/**coccyx** (UBERON:0009832) — caudal appendage.
- **Kidney & urinary tract** (UBERON:0002113) — horseshoe/pelvic kidney, vesicoureteral reflux.
- **Genitalia** (UBERON:0000990) — genital anomalies.
- **Heart** (UBERON:0000948) — congenital heart disease (e.g., PDA).
- **Ear / auditory system** (UBERON:0001690) — hearing loss.
- **CNS** — developmental delay/cognitive impairment (functional).
- **Tissue / cell level:** Connective/skeletal tissue (cartilage, bone) and epithelial (palatal) tissue; the key targeted cell population is the **cranial neural crest cell (CL:0000333)** and its derivatives (chondrocytes, cranial mesenchyme); osteoclasts implicated in skeletal maintenance
(P 41774788).
- **Subcellular level:** Secreted proteins traffic through the **endoplasmic reticulum / secretory pathway** (GO:0005783 ER; GO:0005576 extracellular region); LOF mutations cause ER retention / secretion failure
(P 25912189).
- **Localization / lateralization:** Malformations are typically **bilateral/midline** (bilateral cleft lip/palate, hypertelorism, radioulnar synostosis often bilateral), consistent with a midline/ symmetric developmental patterning defect.

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8. Temporal Development

- **Onset: Congenital** — structural anomalies arise during embryogenesis and are detectable **prenatally** (first prenatal diagnosis: bilateral cleft lip/palate + sacral abnormality + pelvic kidney + brachycephaly;

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P 32441374

Growth deficiency is **postnatal**.

- **Onset pattern:** Non-acute; features are present from birth (insidious/static developmental).
- **Progression:** Non-progressive malformative syndrome; **stable** course. Skeletal contractures or scoliosis may require intervention over time (e.g., knee flexion contracture managed with a Taylor Spatial Frame —

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P 34589314

- **Disease course / duration:** Chronic, lifelong; individuals can survive to adulthood (

P 29407414

describes a 21-year follow-up in an adult).
- **Remission / critical periods:** No remission (structural). The critical window is **embryonic craniofacial neural-crest migration**; interventions are corrective/supportive postnatally rather than preventive of the malformation.

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9. Inheritance and Population

- **Epidemiology:** Ultra-rare; **<50** molecularly confirmed COLEC11/MASP1 patients reported as of 2020 (

P 32441374

), with additional COLEC10 cases since. Formal prevalence/incidence per 100,000 is **not established** (not available).
- **Inheritance: Autosomal recessive** (all three genes) (PMIDs 21258343, 28301481).
- **Penetrance / expressivity:** Presumed high penetrance for a recognizable phenotype in biallelic carriers, but **highly variable expressivity** (mild adult cases lacking cleft/ID/short stature —

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P 29407414

- **Genetic anticipation:** Not applicable (no repeat expansion).
- **Germline mosaicism:** Not reported.

- **Founder effects / consanguinity:** Strong role of **consanguinity**; documented founders — Ashkenazi Jewish COLEC10 c.311G>T (**carrier frequency 1 in 99**, (P 35943032) and Apulian (Italian) COLEC10 c.807_810delCTGT (P 34740859).
- **Carrier frequency:** ≈1.01% in Ashkenazi Jews for the COLEC10 founder allele; otherwise very rare (P 35943032).
- **Population demographics:** Cases reported worldwide (Turkey/Kurdish, Iran, Italy, Mexico, Ashkenazi Jewish, and others), often from consanguineous or founder populations. **Sex ratio:** roughly equal (autosomal; cohort of 7 had 5 F / 2 M — small-sample skew, (P 41703727). **Age distribution:** predominantly diagnosed in infancy/childhood.

10. Diagnostics

- **Clinical recognition:** Diagnosis is suspected on the **facial gestalt** (hypertelorism, blepharophimosis, blepharoptosis, highly arched eyebrows) plus cleft lip/palate and — a relatively specific clue — a **caudal appendage** (PMIDs 34899147, 26789649).
- **Genetic testing (confirmatory, gold standard):**
- **Whole-exome (WES) / whole-genome (WGS) sequencing** or a **3MC/multiple-congenital-anomaly gene panel** covering **MASP1, COLEC11, COLEC10**. Important caveat: some **clinical exome panels omit COLEC10**, causing missed diagnoses — targeted Sanger of COLEC10 may be needed (P 34740859).
- **CNV / deletion analysis:** exon-level and intragenic deletions occur (MASP1) and can be missed by routine pipelines — require careful visual/CNV analysis of WES/WGS (PMIDs 29407414, 41703727).
- Single-gene / Sanger for founder alleles (e.g., Ashkenazi COLEC10 c.311G>T).
- Karyotype/FISH/mtDNA/repeat-expansion testing: not indicated (normal/uninformative).

- **Biomarkers / functional assays:** Serum/plasma **CL-K1 or CL-L1 levels** may be reduced/undetectable with secretion-impairing variants (P 25912189), but levels can be **normal** despite pathogenic variants (P 34740859) — so protein level is supportive, not definitive.
- **Imaging:** Prenatal **ultrasound** (facial clefts + sacral/spinal defect + renal anomaly; P 32441374); postnatal skeletal survey/radiographs (radioulnar synostosis, craniosynostosis, coccygeal appendage); renal ultrasound; echocardiography; audiology; ophthalmologic exam (anterior-segment).
- **Clinical criteria / differential diagnosis:** No formal consensus criteria. Differential includes other blepharophimosis–ptosis syndromes (e.g., BPES), oral-facial-clefting syndromes, Fraser syndrome, and other craniofacial-limb-renal syndromes; the **caudal appendage + radioulnar synostosis + facial gestalt** combination and molecular confirmation distinguish 3MC (P 35943032 notes 3MC should be in the differential for short stature + radioulnar synostosis + cleft lip/palate).
- **Screening: Carrier / cascade screening** in founder populations (Ashkenazi Jewish COLEC10) and consanguineous families; **prenatal molecular testing** feasible once a family variant is known (P 32441374). No newborn-screening program exists.

11. Outcome / Prognosis

- **Survival / mortality:** No formal survival statistics; the disorder is generally **compatible with survival to adulthood** (P 29407414 ,

21-year follow-up). Severe multi-organ involvement (cardiac, renal) can affect prognosis in individual cases.

- **Morbidity / function:** Chronic disability from cognitive impairment, hearing loss, short stature, cleft-related speech/feeding issues, and skeletal/limb constraints (radioulnar synostosis, contractures). Variable — some individuals have mild, near-normal cognition (P 29407414).
- **Quality-of-life measures:** No disease-specific QoL data (not available).
- **Complications:** Cleft-related feeding/speech difficulties and otitis/hearing loss; renal anomalies may predispose to urinary complications; skeletal contractures/scoliosis; psychiatric comorbidity reported (ADHD/ODD/depression; P 37463393).
- **Recovery / prognostic factors:** Malformations are static; outcomes improve with corrective surgery, hearing rehabilitation, and developmental support. Prognosis is modulated by severity of cardiac/renal/CNS involvement. No validated prognostic biomarkers.

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12. Treatment

No disease-modifying or gene-specific therapy exists. Management is multidisciplinary, symptomatic, and supportive.

- **Pharmacotherapy:** None specific to 3MC. Symptomatic (e.g., stimulants/SSRIs for comorbid ADHD/depression as clinically indicated; P 37463393). No pharmacogenomic considerations established. *(NCIT: Supportive Care; Symptomatic Treatment.)*
- **Advanced therapeutics (gene/cell/RNA/targeted/immuno):** None approved or in trials for 3MC (not applicable). The lectin-pathway/CL-11 axis is a therapeutic target in *acquired renal IRI* (L-fucose decoy strategy, P 32472330 , model organism) — not for the developmental syndrome.

- **Surgical / interventional: Cleft lip and palate repair** (NCIT: Cleft Lip Repair / Cleft Palate Repair); craniofacial/craniosynostosis surgery; ptosis/blepharophimosis correction; orthopedic correction of limb contractures/synostosis (e.g., **Taylor Spatial Frame** for knee flexion contracture,
  ); PMID 34589314
  urologic/genital corrective surgery as needed.
- **Supportive / rehabilitative: Hearing aids/audiologic management**; speech therapy; physical/occupational therapy; growth and nutritional monitoring; developmental/educational support; ophthalmologic care.
- **Treatment strategy:** Individualized, coordinated by clinical genetics + craniofacial/plastic surgery, ENT/audiology, orthopedics, urology/nephrology, cardiology, ophthalmology, and developmental pediatrics. **Genetic counseling** is integral.
- **Experimental treatments / trials:** None registered specifically for 3MC (not available).

Suggested NCIT terms: Supportive Care; Surgical Procedure; Cleft Lip Repair; Cleft Palate Repair; Physical Therapy; Genetic Counseling; Hearing Aid.

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13. Prevention

- **Primary prevention:** Not preventable once conceived (congenital genetic disorder). Preconception risk reduction via **genetic counseling** for consanguineous couples and known-carrier families.
- **Secondary prevention / early detection: Prenatal molecular diagnosis** and **prenatal ultrasound** (facial clefts + sacral/renal anomalies) enable early identification and reproductive planning
  ( ). PMID 32441374
  Preimplantation genetic testing (PGT-M) is an option when the familial variant is known.
- **Genetic screening: Carrier and cascade screening** — high-yield in the Ashkenazi Jewish population for COLEC10 c.311G>T (carrier ~1/99) and in consanguineous/founder populations
  ( ). PMID 35943032

- **Counseling:** Autosomal-recessive recurrence risk 25% per pregnancy for carrier couples; molecular confirmation "allows for alternate reproductive options" (P 32441374).
- **Tertiary prevention:** Early cleft repair, hearing rehabilitation, developmental therapy, and orthopedic/urologic surveillance to limit complications.
- **Immunization / public-health / environmental interventions:** Not applicable.

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14. Other Species / Natural Disease

- **Taxonomy of gene orthologs:** MASP1, COLEC11, COLEC10 are conserved in vertebrates — **Mus musculus** (NCBI Taxon 10090), **Danio rerio** (7955), **Homo sapiens** (9606).
- **Naturally occurring animal disease:** No naturally occurring 3MC-equivalent Mendelian disease is catalogued in companion animals/livestock (OMIA — not available). Phenotypes are known only from engineered/experimental models.
- **Comparative biology / conservation:** The lectin complement pathway and its developmental role are evolutionarily conserved; zebrafish colec11/masp1 knockdown reproduces craniofacial and pigmentary defects (P 21258343), demonstrating conserved mechanism.
- **Transmission / zoonosis:** Not applicable (genetic, non-transmissible).

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15. Model Organisms

- **Zebrafish (*Danio rerio*, ZFIN): Morpholino knockdown (morphants)** of *colec11* or *masp1* produce **pigmentary defects and severe craniofacial abnormalities** — the key model recapitulating the human craniofacial phenotype and demonstrating the neural-crest guidance mechanism (P 21258343 , model organism). *Recapitulation: strong for craniofacial/neural-crest features.*

- **Mouse (*Mus musculus*, MGI):**
- **Expression studies:** CL-K1 is highly expressed in embryonic craniofacial cartilage, heart, bronchi, kidney, and vertebral bodies (P 21258343); COLEC10/CL-L1 is expressed in the base membrane of the developing palate (P 28301481) — spatially concordant with affected human structures.
- **Knockouts:** CL-11 (Colec11) knockout alone does **not** reproduce skeletal abnormalities; **combined** CL-11 + MASP-2 / factor B / C3 deficiency causes vertebral bone loss and spinal curvature via impaired osteoclastogenesis (P 41774788 , model organism) — a *limitation* (single-gene mouse KO under-recapitulates the human skeletal phenotype) and a clue that complement modifiers matter.
- **In vitro / cellular models:** Mammalian expression systems demonstrating that disease mutations block CL-K1/CL-L1 secretion and Ca^{2+} binding (PMIDs 25912189, 28301481); **human iPSC-derived osteoclasts** showing CL-11 dependence (P 41774788); recombinant MASP-3 serine-protease domain structural/enzymatic studies (P 23861840).
- **Model limitations:** Mouse single-gene KOs incompletely reproduce the full malformation spectrum (skeletal features require compound complement deficiency); morpholino zebrafish models capture craniofacial/pigment phenotypes but are transient knockdowns.
- **Resources:** ZFIN (zebrafish), MGI/IMPC (mouse), Cellosaurus (iPSC lines).

Evidence Source Summary

Domain	Evidence type	Key PMIDs
Gene discovery (MASP1, COLEC11)	Human + zebrafish + mouse	21258343
Gene discovery (COLEC10)	Human + mouse + in vitro	28301481
Mutation mechanism (secretion, Ca^{2+})	In vitro / structural	25912189, 23861840
Complement pathway link (MASP-3→factor D)	In vitro	27535802, 27782323
Phenotype spectrum & frequencies	Human cohorts/case series	41703727, 36503917, 26789649, 29407414
Founder allele / carrier frequency	Human population	35943032, 34740859, 34636477, 33765348
Prenatal diagnosis	Human case	32441374
Skeletal/osteoclast mechanism	Mouse + iPSC	41774788
Renal CL-11/fucose (adult context)	Mouse / review	31914693, 32472330, 28663231, 27286717
Orthopedic management	Human case	34589314
Psychiatric comorbidity	Human case	37463393

Limitations and Future Directions

- **Ultra-rarity:** <~100 molecularly confirmed patients; frequencies are from small cohorts and case reports, limiting precision of penetrance/expressivity and genotype–phenotype correlation.
- **Genetic heterogeneity:** Some clinically typical, consanguineous patients lack variants in the three known genes

(P 26789649)

— additional lectin-pathway genes likely remain to be discovered.

- **No omics datasets:** No published transcriptomic/proteomic/metabolomic/single-cell profiling of patient tissues; mechanism rests on targeted models and biochemistry.
- **Future directions:** Deeper phenotyping registries; CNV-aware sequencing (to capture exon-level deletions); functional CL-K1/CL-L1 assays as adjunct diagnostics; delineating the neural-crest guidance mechanism at single-cell resolution; exploring complement modifiers of skeletal severity.
