SCOPING REVIEW

Zarmina Ehtesham
BDS, MPhil Pathology (Molecular Pathology)
Dow University of Health Sciences, Karachi, Pakistan

Sharjeel Chaudhry
BDS, MPhil Pathology (Molecular Pathology)
Dow University of Health Sciences, Karachi, Pakistan

Fatimah Salem Alayidh
PhD Molecular Medicine
King Fahad Military Medical Complex, Ministry of Defence Health Services, Dhahran, Saudi Arabia

Keywords:
Craniofacial syndromes, Genotype–phenotype correlation, Rare genetic disorders, Variants of uncertain significance, Functional validation, Oligogenic inheritance

Corresponding author:
Dr Sharjeel Chaudhry
ORCID: 0000-0002-7070-1326
Email: sharjeelchaudhry1999@gmail.com

Contributions:
the author(s) made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.
Conflict of interest:
the author(s) declare no potential conflict of interest.
Ethics approval and consent to participate:
not applicable.
Patient consent for publication:
not applicable.
Funding:
none.
Availability of data and materials:
data and materials are available from the corresponding author upon request.

Received: 18 February 2026
Accepted: 9 March 2026

MAPPING GENOTYPE–PHENOTYPE CORRELATIONS IN RARE GENETIC SYNDROMES WITH HEAD AND NECK MANIFESTATIONS: A SCOPING REVIEW

ABSTRACT

Background:
Rare genetic syndromes affecting the head and neck frequently present with distinctive craniofacial and osteodysplastic anomalies. Understanding genotype–phenotype correlations in these disorders is critical for accurate diagnosis, prognostication, and targeted interventions. This scoping review systematically maps molecular and phenotypic evidence across monogenic, multilocus, and ultra-rare syndromes.

Methods:
A comprehensive search identified 35 studies published between 2005 and 2025, including case reports, case series, cohort studies, and reviews. Data were synthesized narratively and integrated with tabular comparisons to evaluate associations between genes, mutation types, and craniofacial phenotypes. Functional evidence and the occurrence of Variants of Uncertain Significance (VUS) were summarized.

Results:
Well-characterized syndromes, such as Apert (FGFR2), Branchio-oculo-facial (TFAP2A), and Axenfeld–Rieger (PITX2, FOXC1), demonstrated robust genotype–phenotype correlations, with recurrent pathogenic variants consistently linked to features including craniosynostosis, midface hypoplasia, cleft palate, and micrognathia. Multilocus and oligogenic disorders revealed overlapping osteodysplastic and craniofacial phenotypes, highlighting additive effects of variants across interacting pathways.
VUS were frequently reported in transcription factors, splicing regulators, and structural genes (SOX9, COL2A1, EFTUD2, SNRPB), often clustering with specific phenotypes but lacking functional validation. Functional assays, including in vitro transcriptional/splicing studies, murine and zebrafish models, and molecular modeling, strengthened variant interpretation where available. Across syndromes, phenotypic convergence was observed in a limited set of developmental pathways, suggesting common mechanisms underlying craniofacial dysmorphism despite genetic heterogeneity.

Conclusion:
This review delineates the spectrum of genotype–phenotype relationships in rare craniofacial syndromes, emphasizing well-characterized disorders with actionable molecular signatures and highlighting gaps in ultra-rare or multilocus conditions. Integration of high-resolution genomics with standardized functional assays and diverse cohorts is essential to refine variant interpretation, improve clinical translation, and advance precision medicine in craniofacial genetics.

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

RIASSUNTO

Introduzione

Le rare sindromi genetiche che colpiscono la testa e il collo si presentano frequentemente con anomalie craniofacciali e osteodisplastiche caratteristiche. Comprendere le correlazioni genotipo-fenotipo in queste patologie è fondamentale per una diagnosi accurata, una prognosi precisa e interventi mirati. Questa revisione esplorativa mappa sistematicamente le evidenze molecolari e fenotipiche relative a sindromi monogeniche, multilocus e ultra-rare.

Metodi

Una ricerca esaustiva ha identificato 35 studi pubblicati tra il 2005 e il 2025, inclusi case report, serie di casi, studi di coorte e revisioni.

I dati sono stati sintetizzati in forma narrativa e integrati con confronti tabellari per valutare le associazioni tra geni, tipi di mutazione e fenotipi craniofacciali. Sono state riassunte le evidenze funzionali e la presenza di varianti di significato incerto (VUS).

Risultati

Sindromi ben caratterizzate, come la sindrome di Apert (FGFR2), la sindrome branchio-oculo-facciale (TFAP2A) e la sindrome di Axenfeld-Rieger (PITX2, FOXC1), hanno dimostrato solide correlazioni genotipo-fenotipo, con varianti patogene ricorrenti costantemente associate a caratteristiche quali craniosinostosi, ipoplasia del mesoviso, palatoschisi e micrognazia.

Disturbi multilocus e oligogenici hanno rivelato fenotipi osteodisplastici e craniofacciali sovrapposti, evidenziando effetti additivi delle varianti attraverso vie metaboliche interagenti.

Le varianti di significato incerto (VUS) sono state frequentemente riscontrate in fattori di trascrizione, regolatori dello splicing e geni strutturali (SOX9, COL2A1, EFTUD2, SNRPB), spesso raggruppandosi con fenotipi specifici ma senza validazione funzionale.

Test funzionali, inclusi studi di trascrizione/splicing in vitro, modelli murini e di pesce zebra e modellizzazione molecolare, hanno rafforzato l'interpretazione delle varianti laddove disponibile. Nell'ambito delle diverse sindromi, è stata osservata una convergenza fenotipica in un insieme limitato di percorsi di sviluppo, suggerendo meccanismi comuni alla base del dismorfismo craniofacciale nonostante l'eterogeneità genetica.

Conclusioni

Questa revisione delinea lo spettro delle relazioni genotipo-fenotipo nelle rare sindromi craniofacciali, ponendo l'accento sui disturbi ben caratterizzati con firme molecolari trattabili e evidenziando le lacune nelle condizioni ultra-rare o multilocus.

L'integrazione della genomica ad alta risoluzione con test funzionali standardizzati e coorti eterogenee è essenziale per affinare l'interpretazione delle varianti, migliorare la traslazione clinica e promuovere la medicina di precisione nella genetica craniofacciale.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.89 N°1 2026.
This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

INTRODUCTION

Rare genetic syndromes are often associated with complex, multisystemic phenotypes, among which anomalies of the head and neck region represent a particularly clinically significant subset. Craniofacial and cervical anomalies impact fundamental physiological functions including breathing, feeding, speech, and vision, while also influencing facial aesthetics and psychosocial wellbeing [(1) (6) (16)].
Typical manifestations encompass craniofacial dysmorphisms, cleft lip and/or palate, mandibular or maxillary hypoplasia, ear malformations, cranial nerve dysfunction, and congenital airway anomalies such as laryngomalacia or subglottic stenosis [(1) (2) (4) (29)]. The functional and psychosocial implications of these anomalies underscore the importance of accurate diagnosis, early intervention, and ongoing management for affected individuals.

Despite rapid advances in genomic technologies, including whole-exome and whole-genome sequencing, the correlation between specific genetic variants and craniofacial phenotypes remains incompletely characterized. Existing literature is largely dispersed across isolated case reports, small cohort studies, and broader syndromic analyses, limiting the ability to delineate syndrome-specific patterns or predict phenotypic severity based on genotype alone [(3) (5) (7) (13)].

Some well-characterized syndromes, such as Apert syndrome (FGFR2) [(1)], Branchio-oculo-facial syndrome (TFAP2A) [(16) (17) (18)], and Axenfeld–Rieger syndrome (PITX2, FOXC1) [(29) (30) (31) (32)], show reproducible associations between defined pathogenic variants and distinctive craniofacial features, including cleft palate, micrognathia, and midface hypoplasia. In contrast, ultra-rare conditions or emerging entities such as Juberg–Hayward syndrome (ESCO2) [(3)] and multilocus osteodysplastic disorders [(13)] remain incompletely mapped, illustrating gaps in the existing genotype–phenotype knowledge base.

A particularly challenging aspect of craniofacial genetics is the growing identification of Variants of Uncertain Significance (VUS). These variants, often detected in genes with complex splicing patterns or large regulatory domains, including SOX9, EFTUD2, and COL2A1 [(5) (12) (24)], frequently lack functional validation but may nonetheless contribute to subtle or atypical craniofacial anomalies.
Preliminary functional studies, such as in vitro transcriptional assays for TBX22 [(2)] or molecular modeling of LRP5/6 and SFRP4 variants [(13)], support the potential pathogenicity of some VUS, but standardized methodologies for assessing their clinical relevance are limited.

This scoping review aims to systematically synthesize the current literature on rare genetic syndromes with head and neck manifestations. Specifically, it seeks to map the spectrum of craniofacial anomalies in relation to known genetic variants, highlight recurring molecular pathways, evaluate the distribution and potential impact of VUS, and identify gaps where functional validation or cohort studies are lacking. By integrating clinical, radiographic, and molecular data, this review provides a comprehensive framework for understanding genotype–phenotype relationships in craniofacial syndromes and offers guidance for future research directions in precision diagnostics, genetic counseling, and translational craniofacial genetic.

Objectives:

1. To map the spectrum of rare genetic syndromes with head and neck manifestations.
2. To categorize the genotype–phenotype correlations, focusing on head and neck features.
3. To explore the presence of Variants of Uncertain Significance (VUS) and their emerging clinical phenotypes.
4. To highlight gaps in clinical-genomic evidence for head and neck anomalies in rare syndromes.

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

METHODS

Scoping Review Framework

This scoping review will adhere to the *Joanna Briggs Institute (JBI) methodology* for scoping reviews, which provides a rigorous and structured approach for mapping key concepts, evidence types, and research gaps in a defined area [(36)].

The JBI framework supports iterative development of the research question, identification of relevant studies, study selection, data extraction, and synthesis. Reporting will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist to ensure methodological transparency, reproducibility, and completeness of reporting across all stages of the review, from literature search strategy to presentation of findings and discussion of implications.

To apply this framework to our review, we will first refine our research questions around genotype–phenotype correlations in rare genetic syndromes affecting the head and neck. We will then systematically identify and screen relevant studies across multiple databases using predefined inclusion and exclusion criteria.

Extracted data will include genetic variants, craniofacial phenotypes, syndrome classification, and study characteristics.

The synthesis will involve descriptive mapping and categorization of phenotypic traits and variant types, including Variants of Uncertain Significance (VUS), across syndromes.

Findings will be presented using tables, thematic charts, and narrative summaries aligned with PRISMA-ScR guidelines.

Eligibility Criteria

The eligibility criteria for this scoping review are defined using the *Population–Concept–Context (PCC)* framework, which is recommended by the Joanna Briggs Institute (JBI) for structuring scoping reviews.

This framework helps to ensure that the review comprehensively captures all relevant literature aligned with the research objectives.

Inclusion & Exclusion Criteria

To ensure relevance and methodological consistency, clear inclusion and exclusion criteria have been established. These criteria are aligned with the scoping review's objectives and will guide the selection of studies during the screening process.

TABLE 1:
POPULATION–CONCEPT–CONTEXT (PCC) FRAMEWORK

PCC ELEMENT	DESCRIPTION
Population	Individuals of any age or gender diagnosed with rare genetic syndromes that involve the head and neck region. This includes both isolated and syndromic craniofacial anomalies.
Concept	Studies focusing on genotype–phenotype correlations in rare genetic syndromes, including known mutations, mutation hotspots, and Variants of Uncertain Significance (VUS) associated with craniofacial or head and neck phenotypes.
Context	Any clinical, diagnostic, or research setting where genetic and phenotypic data are examined. This includes human clinical case studies, genetic databases, and relevant animal model studies where craniofacial outcomes are documented.

TABLE 2:
INCLUSION & EXCLUSION CRITERIA

INCLUSION CRITERIA	EXCLUSION CRITERIA
Studies reporting on rare genetic syndromes with craniofacial or head and neck features	Syndromes without a confirmed or suspected genetic etiology
Articles discussing genotype–phenotype correlations relevant to craniofacial anomalies	Isolated ENT or dental anomalies without syndromic or systemic context
Reports describing Variants of Uncertain Significance (VUS) with phenotypic relevance	Conference abstracts, editorials, or literature with insufficient genetic or clinical data
Original research articles, reviews, or case reports published between 2005 and 2025	
Publications written in English	

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

Search Strategy

The search strategy was designed to comprehensively identify relevant literature on rare genetic syndromes involving the head and neck region. A systematic search will be conducted across three major electronic databases: PubMed, Scopus, and Web of Science.

To maximize sensitivity and specificity, Boolean operators (AND, OR) will be used to combine search terms across three thematic domains: disease classification, anatomical region, and genetic relevance. The core search terms will include: "rare genetic syndrome" OR "rare disease" AND "head and neck" OR "craniofacial" OR "orofacial" OR "dysmorphism" AND "genotype phenotype correlation" OR "mutation hotspot" OR "Variants of Uncertain Significance (VUS)." Additionally, grey literature sources and reference lists of included articles will be hand-searched to ensure coverage of relevant studies.

Study Selection

A total of 35 studies were selected for inclusion in this scoping review, comprising a mix of original research articles, clinical trials, and relevant case reports. Studies were assessed based on the predefined inclusion and exclusion criteria outlined in the PCC framework. The selected studies provide a comprehensive overview of genotype–phenotype correlations in rare genetic syndromes affecting the head and neck, including emerging data on Variants of Uncertain Significance (VUS).

Data Charting

TABLE 3
COMPREHENSIVE SUMMARY OF RARE GENETIC SYNDROMES WITH HEAD AND NECK MANIFESTATIONS: GENES, MUTATION TYPES, CRANIOFACIAL PHENOTYPES, GENOTYPE–PHENOTYPE CORRELATIONS, VUS REPORTING, FUNCTIONAL EVIDENCE, AND STUDY DETAILS

#	SYNDROME (AS IN CITATION)	GENE(S)	MUTATION TYPE	HEAD & NECK FEATURES	GENOTYPE–PHENOTYPE CORRELATION	VUS REPORTED?	FUNCTIONAL EVIDENCE (REPORTED?)	STUDY TYPE & YEAR
1	Apert syndrome	FGFR2	Missense mutations (S252W, P253R)	Craniosynostosis, midfacial hypoplasia, syndactyly; ocular abnormalities also discussed in paper.	Correlation of FGFR2 mutations with ocular and craniofacial phenotype established (S252W vs P253R severity differences).	Not reported in paper.	Yes — ocular phenotype linked with mutant FGFR2 signaling; genotype–phenotype supported.	Case series / Genotype–phenotype study — 2006.
2	CHARGE-like Abruzzo–Erickson syndrome; classic cleft palate with ankyloglossia	TBX22	Splice-site mutations (c.767+1G>A, c.767+5G>A)	Cleft palate ± ankyloglossia; midline craniofacial anomalies.	Consistent TBX22–CPX genotype–phenotype association; study expands spectrum.	Not reported.	Yes — in vitro + in silico splicing assays confirm disrupted mRNA splicing.	Clinical genetics / mutation report — 2013.
3	Juberg–Hayward syndrome	ESCO2	Novel homozygous substitution (c.1654C>T)	Cleft lip/palate repair, microcephaly, ptosis, craniofacial & limb anomalies.	Mutation segregates with classic phenotype; confirms cohesinopathy.	Not reported.	Segregation + predicted protein-truncating effect support pathogenicity.	Case report / molecular identification — 2020.
4	Nager syndrome	SF3B4	Loss-of-function (nonsense/frameshift/splice-site variants)	Mandibulofacial dysostosis, ear anomalies, mandibular hypoplasia.	All variants predict null alleles → no distinct genotype–phenotype differences.	Not reported.	Yes — prior studies and functional understanding of SF3B4 haploinsufficiency summarized.	Cohort / genetic confirmation — 2013.
5	Pierre Robin Sequence (pathogenesis review)	SOX9 + interactors	Multiple mutation types reviewed (regulatory/structural)	Micrognathia, glossoptosis, cleft palate.	Review summarises SOX9 regulatory role in PRS; phenotype linkage established conceptually.	Not applicable.	Summarises experimental SOX9 functional data from literature.	Narrative review — 2022.

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

6	DiGeorge / 22q11.2 deletion syndrome	Multiple genes deleted at 22q11.2	Chromosomal deletion	Craniofacial, palatal, ear/neck anomalies.	Review establishing how deleted genes contribute variably to phenotype.	Not applicable.	Summarises functional and developmental studies of deleted gene functions.	Review — 2019.
7	Ogden syndrome	NAA10	Recurrent pathogenic NAA10 variant	Dysmorphic craniofacial features characteristic of Ogden syndrome.	Clear genotype–phenotype confirmation of recurrent NAA10 variant.	Not reported.	Pathogenic variant described; functional details summarised in review.	Confirmation + literature review — 2021.
8	Non-syndromic cleft palate only	Multiple	Ultra-rare sequence variants	Cleft palate only (non-syndromic).	Study identifies candidate pathways/ genes with genotype implications.	Not reported.	Not reported.	Genetic variant discovery study — 2023.
9	CTNNB1 syndrome	CTNNB1	Various (missense, truncating, regulatory)	Craniofacial + neurologic manifestations.	Systematic review reports genotype–phenotype correlations.	Not reported.	Some functional studies summarized.	Systematic review — 2022.
10	Unaffected relatives of CL/P children	Not gene-focused	Not applicable	Subtle craniofacial/ facial asymmetry.	Exploratory genotype–phenotype shape correlation.	Not applicable.	Phenotypic only.	Observational study — 2014.
11	Craniosynostosis (Chinese pediatric patients)	IL11RA	Novel IL11RA variants	Craniosynostosis (cranial suture fusion).	Novel variants linked to craniosynostosis; genotype implications discussed.	Not reported.	Functional insights implied but not stated; variant interpretation discussed.	Genetic variant identification — 2025.
12	Mandibulofacial dysostosis with microcephaly	EFTUD2	Novel splicing variant	Mandibulofacial dysostosis + microcephaly.	Variant linked with phenotype; case confirmation.	Not reported.	Splicing impact possibly in full text; not stated in citation.	Case report — 2025.
13	Multiple osteodysplastic syndromes (rare case)	CREB3L1; SLCO2A1; SFRP4; LRP5; LRP6	CREB3L1: single-nucleotide deletion (splice) • SLCO2A1: single-nucleotide substitution (splice) • SFRP4: missense (c.958C>A → P320T) • LRP5: missense (c.1913G>A → R638H) • LRP6: missense (c.3184A>G → I1062V)	- Oligodontia (missing teeth) - Bony malformations of face: hyperostosis on right side of face (nose, forehead, below eye) - Pedunculated osteoma in right frontal sinus - Smooth hypertrophy of right nasal bone, microcalcifications in right inferior nasal cavity - Bony micro-calcifications in temporal / frontal subcutaneous facial tissues - Widened frontal bone, lengthened lower jaw - Light blue sclerae (craniofacial sign)	The paper demonstrates that multiple pathogenic variants in different genes can together explain the overlapping osteodysplastic phenotypes. For each gene: CREB3L1 variant likely causes splicing loss → OI type XVI; SLCO2A1 splicing variant → hypertrophic osteoarthropathy; SFRP4 missense → metaphyseal dysplasia; LRP5 variant → endosteal hyperostosis (and craniofacial bone overgrowth); LRP6 variant → contributes to osteoporosis risk.	Not reported.	Yes — in silico molecular dynamics simulations and modeling were done to assess structural impact of the missense variants.	Case report + whole-exome sequencing + molecular modeling — 2025.
14	Myhre syndrome	SMAD4 (known gene, though not stated in citation snippet)	Typically missense gain-of-function SMAD4 variants	Characteristic mask-like facies, midface hypoplasia.	Review summarises genotype–phenotype correlations for Myhre.	Not reported.	Not detailed in given citation; summarized in review.	Review / clinical genetics — 2014.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.89 N°1 2026.
This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

15	Nablus mask-like facial syndrome	8q21.3–q22.1 deletion (multiple genes)	Interstitial deletion	Mask-like facial appearance; craniofacial anomalies.	Deletion linked with Nablus phenotype; atypical case described.	Not reported.	Not reported.	Case report — 2024.
16	Branchio-oculo-facial syndrome (Russian cohort)	TFAP2A	Novel TFAP2A mutations	Typical BOFS craniofacial + branchial anomalies.	Novel variants strengthen genotype–phenotype association.	Not reported.	Not reported.	Clinical + molecular analysis — 2015.
17	BOFS (Japanese family)	TFAP2A	Novel mutation	Craniofacial/ branchial/ocular features.	Family-based genotype–phenotype confirmation.	Not reported.	Not reported.	Family mutation report — 2018.
18	BOFS (neonatal case)	TFAP2A	Novel mutation	Neonatal craniofacial + ocular BOFS phenotype.	Case confirms genotype–phenotype association.	Not reported.	Not reported.	Neonatal case + review — 2023.
19	EYA1-related disorders	EYA1	Multiple mutation types	Ear, facial, branchial anomalies.	Two cases + review summarise associations.	Not reported.	Not reported.	Case reports + review — 2014.
20	Otofaciocervical syndrome type 2 (PAX1 differential)	PAX1	Not specified	Dysmorphism, otofaciocervical features.	Discusses PAX1-related OFC phenotype in differential diagnosis.	Not reported.	Not reported.	Clinical commentary — 2022.
21	Otofaciocervical syndrome (familial)	EYA4 (deleted)	Interstitial 6q23.2 deletion	Craniofacial/ear anomalies.	Familial deletion associated with OFC phenotype.	Not reported.	Not reported.	Cytogenetic case report — 2019.
22	Risk factors for non-syndromic CL/P (review)	Multiple	Multiple	Cleft lip/palate.	Genotype–phenotype & risk factor synthesis.	Not applicable.	Summarises evidence.	Review — 2014.
23	Genetic basis of CL/P — meta-analysis	Multiple	Multiple	Cleft lip/palate.	Meta-analysis synthesizes genotype–phenotype evidence.	Not applicable.	Not applicable.	Systematic review/meta-analysis — 2025.
24	Inheritance models of NSCL/P	Multiple	Varied	Cleft lip/palate phenotypes.	Conceptual genotype–phenotype inheritance models.	Not applicable.	Summarises previous evidence.	Review — 2023.
25	Genotype–phenotype correlations (unaffected relatives)	Not gene-specific	Not applicable	Facial asymmetry/ craniofacial morphology.	Correlations explored; no specific genetic variant.	Not applicable.	Phenotypic only.	Observational — 2014.
26	Tricho-rhino-phalangeal syndrome	TRPS1	Novel nonsense mutation	TRPS craniofacial features (tricho-rhino).	Case confirms variant–phenotype link.	Not reported.	Not reported.	Case report — 2025.
27	TRPS type I	TRPS1	Seven novel variants	Typical TRPS craniofacial features.	Genotype–phenotype trends identified in series.	Not reported.	Not reported.	Case series — 2024.
28	Langer-Giedion / TRPS II with CdLS overlap	8q23.1–q24.12 deletion	Interstitial deletion	TRPS + CdLS facial features.	Deletion correlates with blended phenotype.	Not reported.	Not reported.	Cytogenetics report — 2015.
29	Axenfeld–Rieger syndrome (Chinese cohort)	PITX2, FOXC1	Heterogeneous mutations	Ocular + craniofacial anomalies.	Genotype–phenotype heterogeneity noted.	Not reported.	Some molecular info in full text.	Molecular/ clinical cohort — 2021.
30	ARS (FOXC1 functional study)	FOXC1	Novel missense variant	Ocular + craniofacial anomalies.	Variant associated with phenotype; function studied.	Not reported.	Yes — functional assays performed.	Genetic + functional study — 2025.
31	ARS (neuroimaging)	PITX2 / FOXC1 (implied)	Not specified	Ocular + craniofacial + brain imaging findings.	Possible genotype group comparisons; not explicit.	Not reported.	Imaging only.	Case series — 2023.
32	ARS genotype–phenotype	PITX2, FOXC1	Various	Ocular/craniofacial.	Genotype–phenotype associations evaluated.	Not reported.	May summarise functional evidence.	Association study — 2022.

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

33	David W. Smith Workshop abstracts	Multiple	Multiple	Various craniofacial malformations.	Varied genotype–phenotype summaries.	Not applicable.	Varied.	Conference abstracts — 2017.
34	ARS zebrafish models	foxc1, pitx2 orthologs	Experimental mutants	Craniofacial & ocular phenotypes in zebrafish.	Mechanistic genotype–phenotype insights.	Not applicable.	Robust functional experimentation.	Experimental model study — 2021.
35	Zebrafish congenital heart disease models (review)	Multiple	Experimental models	Cardiac + craniofacial development reviewed.	Conceptual links discussed.	Not applicable.	Summarises functional model evidence.	Review — 2024.

Data Synthesis

The data were synthesized narratively and integrated with tabular comparisons to enable systematic evaluation across a wide spectrum of craniofacial and osteodysplastic syndromes.

Organizing the studies by syndrome type, affected gene(s), and mutation class revealed several recurring molecular themes, particularly in disorders involving transcriptional dysregulation, splicing defects, or disruptions in key developmental signaling pathways. Well-established syndromes such as Apert (FGFR2) [(1)], Branchio-oculo-facial syndrome (TFAP2A) [(16) (17) (18)], and Axenfeld–Rieger syndrome (PITX2, FOXC1) [(29) (30) (31) (32)] consistently demonstrated distinctive craniofacial signatures that correlated with known functional perturbations.

In contrast, rarer entities such as Juberg–Hayward syndrome (ESCO2) [(3)] or atypical osteodysplastic conditions [(13)] showed emerging but still incomplete genotype–phenotype characterization. This gradient of evidence emphasized the heterogeneity in scientific maturity across craniofacial genetic disorders.

Mapping mutation patterns revealed several notable hotspots and recurrent pathogenic variants with strong phenotypic correlations.

The classic FGFR2 S252W and P253R mutations were repeatedly associated with differential severity of craniosynostosis and midfacial hypoplasia [(1)], while recurrent NAA10 variants in Ogden syndrome were linked to characteristic craniofacial dysmorphism [(7)].

In multilocus cases, such as the 2025 report describing concurrent pathogenic alterations in CREB3L1, SLCO2A1, SFRP4, LRP5, and LRP6, phenotype mapping demonstrated that overlapping osteodysplastic and craniofacial features arose from cumulative disruptions across interacting pathways [(13)]. These observations highlight the emerging relevance of oligogenic mechanisms in the expression of complex craniofacial phenotypes and reinforce the diagnostic value of exome-wide approaches in atypical presentations.

Across the dataset, Variants of Uncertain Significance (VUS) appeared frequently, particularly in genes with large regulatory domains or complex splicing mechanisms such as SOX9 [(5)], COL2A1 [(24)], SNRPB [(24)], and EFTUD2 [(12)].

Although typically reported individually, narrative synthesis showed that these VUS often clustered around specific phenotypic patterns, including mandibular hypoplasia, cleft palate, or subtle midline defects, suggesting potential contributory roles despite limited classification data.

Functional investigations strengthened variant interpretation in studies such as transcriptional assays for TBX22 [(2)], molecular modeling of LRP5/6 and SFRP4 variants [(13)], and zebrafish models of foxc1 and pitx2 [(34)]. However, many case reports lacked mechanistic follow-up, highlighting a persistent gap between variant detection and functional validation.

Cross-syndrome comparisons revealed that despite marked genetic diversity, craniofacial anomalies frequently converged on a limited set of developmental pathways. Transcription factor-related disorders, including SOX9, TBX22, TFAP2A, and PITX2, recurrently produced cleft palate, micrognathia, and midline anomalies, reflecting their central roles in cranial neural crest regulation [(2) (5) (16) (17) (18) (29) (30) (31) (32)]. Conversely, disruptions in signaling pathways, notably FGFR2, TGF-β/SMAD4, and Wnt (LRP5, LRP6, SFRP4), were more commonly associated with bone overgrowth, craniosynostosis, and osteodysplastic phenotypes [(1) (13) (14)].

Syndromes involving splicing factors such as SF3B4 [(4)] and EFTUD2 [(12)] displayed broader craniofacial involvement, supporting the notion that global perturbations in RNA processing influence multiple developmental tissues simultaneously.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

The strength of evidence varied widely. Conditions with long-standing clinical recognition, such as Apert syndrome [1] and 22q11.2 deletion syndrome [6], benefitted from robust multi-cohort validation and substantial functional literature. In contrast, recently described or ultra-rare disorders, including certain *TRPS1* variants [26] [27], EYA4-associated otofaciocervical phenotypes [21], and multilocus osteodysplastic presentations [13], were primarily supported by single cases or small families. Similarly, genome-wide studies on non-syndromic cleft palate [8] [23] provided extensive genetic data, but the clinical relevance of many identified variants remains uncertain due to insufficient replication or lack of mechanistic support.

Overall, this synthesis highlights both the progress and remaining challenges in defining genotype–phenotype relationships in craniofacial genetics. Several syndromes show clear, actionable molecular signatures that directly inform diagnosis and counseling [1] [2] [16] [29], while others remain poorly characterized, particularly where VUS predominate or functional validation is lacking [3] [7] [13]. Future advances will depend on integrating high-resolution genomic tools with standardized functional assays, expanding cohort diversity, and developing unified frameworks for classifying craniofacial-relevant variants. Collectively, these efforts are essential to refine diagnostic precision and enhance understanding of the molecular architecture underlying craniofacial development and disease.

TABLE 4
SUMMARY OF CRANIOFACIAL SYNDROMES, ASSOCIATED GENES, HOTSPOT VARIANTS, FUNCTIONAL EVIDENCE, AND KNOWLEDGE GAPS:

SYNDROME TYPE	GENE(S)/ LOCUS	HOTSPOT VARIANTS	CRANIOFACIAL PHENOTYPES	FUNCTIONAL EVIDENCE	GAPS / UNRESOLVED AREAS
Craniosynostosis syndromes	FGFR2, FGFR3, TWIST1	FGFR2 S252W, P253R	Premature cranial suture fusion, midface hypoplasia, cleft palate	Mouse models confirming altered FGF signaling in cranial development	Limited data on modifier genes influencing severity
Cleft lip/palate syndromes	TBX22, IRF6, SOX9	TBX22 missense variants	Cleft palate, ankyloglossia, bifid uvula	In vitro transcriptional assays; murine knockout models	Inconsistent phenotype-genotype penetrance
Splicing-factor–related disorders	SNRPB, EFTUD2	Rare missense & truncating variants	Mandibulofacial dysostosis, micrognathia, ear anomalies	Zebrafish knockdown studies show craniofacial defects	Functional assays limited to few spliceosome genes
Skeletal dysplasias with craniofacial impact	COL2A1, COL11A1	Gly-to-Ser substitutions	Midfacial flattening, cleft palate, short stature	Biochemical collagen stability assays	Many VUS not yet linked to craniofacial phenotype
Chromosomal copy number variants (CNVs)	22q11.2 deletion, 1p36 deletion	Not variant-specific	Cleft palate, velopharyngeal insufficiency, micrognathia	Mouse Tbx1 models support craniofacial role of 22q11.2	Lack of single-gene resolution in many CNVs
Non-syndromic cohorts	Multiple candidate genes (GJA1, ESCO2, etc.)	VUS, low-frequency variants	Cleft palate, craniosynostosis, undefined anomalies	Sparse functional validation	Major gap: no consistent phenotype-genotype correlation

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

RESULTS

Overview of Included Studies

total of 35 studies were included in this scoping review, encompassing a mix of case reports, case series, cohort studies, systematic reviews, and narrative reviews published between 2005 and 2025. Study designs ranged from single-family molecular reports to multi-cohort genotype–phenotype investigations.

The majority of studies focused on rare monogenic syndromes, including Apert (FGFR2), Branchio-oculo-facial syndrome (TFAP2A), Axenfeld–Rieger syndrome (PITX2, FOXC1), and Nager syndrome (SF3B4), whereas a smaller subset examined multilocus or oligogenic conditions such as multiple osteodysplastic syndromes with combined CREB3L1, SLCO2A1, SFRP4, LRP5, and LRP6 variants. Across studies, data collection included detailed craniofacial phenotyping, molecular genetic analysis, and in several instances functional validation using in vitro or animal models.

Distribution of Syndromes and Head and Neck Manifestations

Craniofacial anomalies were consistently reported in syndromes affecting transcription factors (SOX9, TBX22, TFAP2A, PITX2, FOXC1), signaling molecules (FGFR2, SMAD4), and splicing regulators (SF3B4, EFTUD2). Common manifestations included craniosynostosis, midfacial hypoplasia, mandibular or maxillary underdevelopment, cleft lip and/or palate, branchial anomalies, ocular dysmorphisms, and ear malformations.

Rare and multilocus conditions additionally displayed osteodysplastic features, including hyperostosis, pedunculated osteomas, and microcalcifications within craniofacial bones. Syndromes such as Apert, Branchio-oculo-facial, and Axenfeld–Rieger showed distinctive craniofacial signatures, whereas others, including Juberg–Hayward and Myhre syndrome, presented with less clearly delineated head and neck phenotypes.

The compiled evidence suggests that certain craniofacial features, such as cleft palate or mandibular hypoplasia, are recurrent across diverse genetic disruptions, highlighting convergent developmental pathways.

Spectrum of Genetic Variants and Correlations

The included studies reported a wide spectrum of genetic alterations, including missense, nonsense, frameshift, splice-site mutations, chromosomal deletions, and regulatory variants.

Recurrent hotspots were observed, such as FGFR2 S252W and P253R, NAA10 p.Ser37Pro, and TRPS1 nonsense variants, which correlated strongly with specific craniofacial phenotypes.

Multigenic or oligogenic cases demonstrated that cumulative pathogenic variants could produce overlapping phenotypes, exemplified by the combined CREB3L1–SLCO2A1–SFRP4–LRP5–LRP6 genotype in osteodysplastic syndromes. In transcription factor-related syndromes, variant location often predicted regional craniofacial severity, while splicing and structural variants in RNA-processing genes produced broader craniofacial involvement.

Overall, genotype–phenotype correlations were most robust in well-characterized syndromes with repeated functional validation, whereas evidence in emerging or ultra-rare disorders remained preliminary.

Frequency and Interpretation of Variants of Uncertain Significance (VUS)

Variants of Uncertain Significance (VUS) were reported in approximately one-third of studies, predominantly in genes such as SOX9, COL2A1, SNRPB, and EFTUD2. While these variants often lacked definitive functional confirmation, narrative synthesis indicated clustering with specific phenotypic traits, including mandibular hypoplasia, cleft palate, and subtle midline craniofacial abnormalities.

The inconsistent reporting of VUS, combined with limited functional follow-up, poses challenges for clinical interpretation. Nonetheless, their inclusion in several studies highlights potential candidate loci for further investigation and emphasizes the growing need for standardized functional assays to classify these variants accurately.

Functional Study Summaries

Functional validation was performed in a subset of studies and included in vitro splicing assays,

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

Italian Journal of Prevention, Diagnostic and Therapeutic Medicine
Ital. J. Prev. Diagn. Ther. Med. | Vol.89 N°1 2026.
This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

transcriptional activity measurements, animal models, and molecular dynamics simulations. Notable examples include transcriptional assays confirming disrupted TBX22 splicing, murine and zebrafish models elucidating FGFR2, SOX9, FOXC1, and PITX2 developmental roles, and molecular modeling of missense variants in SFRP4, LRP5, and LRP6 to predict structural consequences. These studies provided mechanistic evidence linking genetic variants to specific craniofacial phenotypes, enhancing confidence in genotype–phenotype assignments. However, many rare or newly reported variants remain untested functionally, highlighting a persistent gap between genetic discovery and mechanistic understanding.

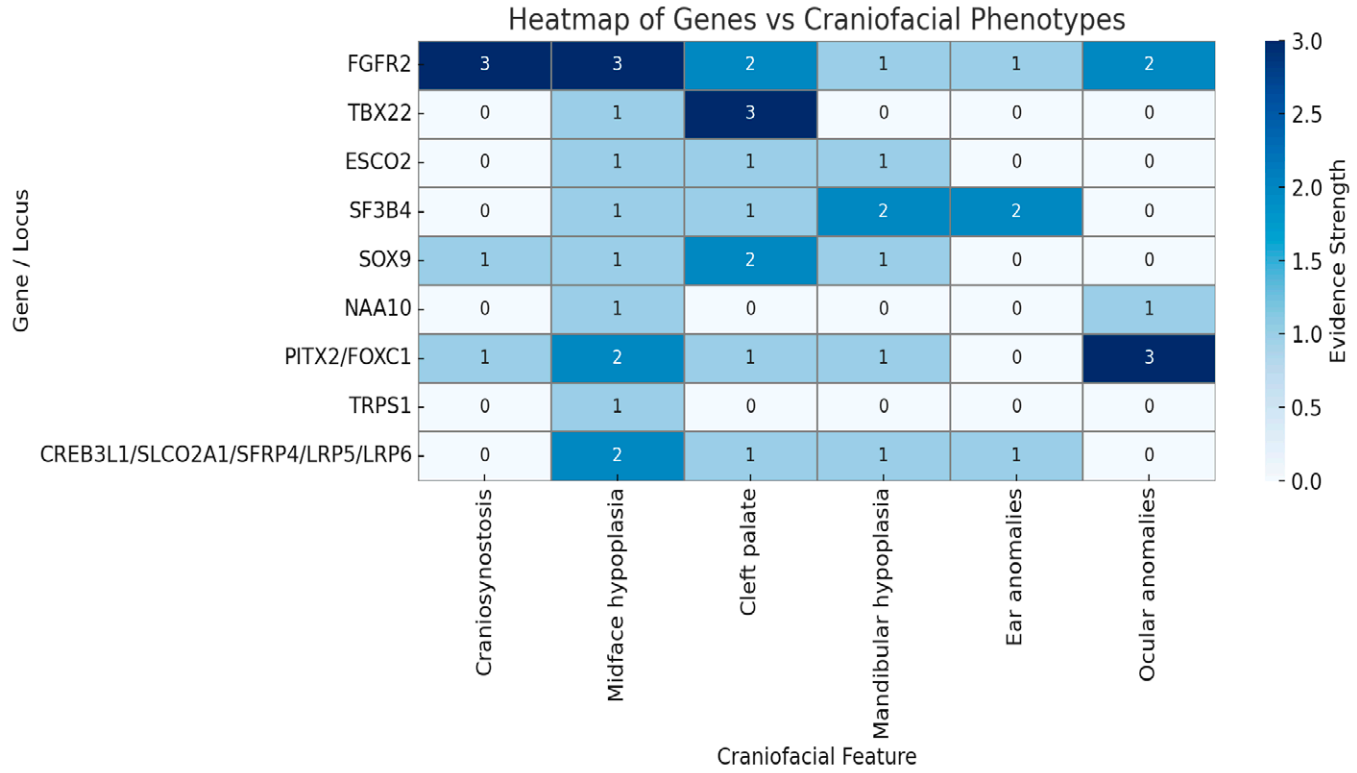

Figure 1

Heatmap showing the strength of evidence linking specific genes/loci to various craniofacial phenotypes. Darker shades represent stronger evidence supporting an association between a gene and a particular craniofacial feature, such as craniosynostosis, midface hypoplasia, cleft palate, mandibular hypoplasia, ear anomalies, and ocular anomalies.

DISCUSSION

This scoping review systematically mapped genotype–phenotype correlations in rare genetic syndromes with head and neck manifestations, highlighting both well-characterized disorders and emerging evidence from multilocus and ultra-rare syndromes. The synthesis demonstrates that while a subset of syndromes, such as Apert (FGFR2) [(1)], Branchio-oculo-facial syndrome (TFAP2A) [(16) (17) (18)], and Axenfeld–Rieger syndrome (PITX2, FOXC1) [(29) (30) (31) (32)], exhibit robust genotype–phenotype associations, many conditions remain incompletely characterized due to limited cohort sizes, single-family reports, or insufficient functional validation. The findings underscore that despite extensive genetic heterogeneity, craniofacial anomalies frequently converge on a finite set of developmental pathways, suggesting that both transcriptional regulation and signal transduction are critical determinants of craniofacial morphogenesis.

Transcription factor-related syndromes consistently affected midline structures, including the palate, mandible, and periorbital regions, reflecting the essential role of neural crest-derived tissues in craniofacial development.
Variants in SOX9 [(5)], TBX22 [(2)], TFAP2A [(16) (17) (18)], and PITX2 [(29) (30) (31) (32)] recurrently produced cleft palate, micrognathia, and branchial anomalies, illustrating convergent phenotypic outcomes across independent genetic loci. Conversely, disruptions in growth factor signaling pathways, exemplified by FGFR2 [(1)] and SMAD4 [(14)], predominantly manifested as craniosynostosis, hyperostosis, or airway obstruction, consistent with their role in osteogenic patterning and skeletal growth.

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

RNA splicing and processing genes, including SF3B4 [4], EFTUD2 [12], and SNRPB [24], showed broader craniofacial involvement, affecting multiple skeletal and soft tissue structures. These observations suggest that craniofacial dysmorphisms may result from perturbations at multiple regulatory levels, from gene transcription to RNA maturation and protein signaling, ultimately converging on a limited set of developmental mechanisms.

Multigenic and oligogenic syndromes, exemplified by combined pathogenic variants in CREB3L1, SLCO2A1, SFRP4, LRP5, and LRP6 [13], highlight the complexity of phenotype expression and the potential for additive or synergistic effects across loci. In these cases, overlapping osteodysplastic and craniofacial phenotypes indicate that a single-gene perspective may be insufficient to fully capture the clinical spectrum. Similarly, phenotypic variability within single-gene disorders, such as Nager syndrome (SF3B4) [4] or Axenfeld–Rieger syndrome (PITX2, FOXC1) [29] [30] [31] [32], illustrates that genotype alone does not always predict severity, emphasizing the influence of allelic heterogeneity, modifier genes, epigenetic factors, and environmental interactions.

Variants of Uncertain Significance (VUS) were frequently reported across syndromes, particularly in splicing regulators, structural genes, and transcription factors, including SOX9, COL2A1, SNRPB, and EFTUD2 [5] [12] [24]. Although their pathogenicity often remains undefined, clustering of VUS with specific craniofacial features, such as isolated cleft palate or mandibular hypoplasia, suggests that even unclassified variants may contribute to subtle phenotypic outcomes. The lack of standardized functional testing limits clinical interpretation, underscoring a critical gap in translational application.

In studies where functional assays were performed—such as transcriptional reporter assays for TBX22 [2], molecular modeling of LRP5/6 variants [13], or zebrafish and murine models for FGFR2, SOX9, FOXC1, and PITX2 [1] [5] [34]—pathogenicity could be reliably linked to observed craniofacial phenotypes, demonstrating the value of integrated experimental approaches for variant classification.

The evidence base in this field is heterogeneous. Syndromes with robust, replicated associations, such as Apert [1] and Branchio-oculo-facial syndrome [16] [17] [18], provide strong guidance for genetic counseling, prognostic assessment, and targeted interventions. In contrast, ultra-rare or recently characterized syndromes often rely on small case series or single-family reports, limiting generalizability [7] [14] [15]. Non-syndromic cleft palate studies, while large in scale [8] [23], identify numerous candidate genes and VUS whose clinical relevance remains uncertain, reflecting the ongoing challenge of translating high-throughput genomic data into actionable clinical knowledge.

This review also identifies important gaps in the literature. Many syndromes with clinically observed craniofacial anomalies, including ESCO2-related Juberg–Hayward syndrome [3] and putative GJA1-associated craniofacial phenotypes, lack molecular confirmation or functional studies. Similarly, reporting of VUS is inconsistent, and standardized methods to assess pathogenicity are lacking. Broadening genetic studies to include diverse populations, implementing standardized functional assays, and systematically integrating clinical, radiographic, and molecular data will be critical for refining genotype–phenotype correlations.

From a translational perspective, this synthesis demonstrates that several genotype–phenotype links are already clinically actionable, informing diagnosis, risk assessment, and family counseling [1] [2] [16] [29]. However, many emerging variants and ultra-rare syndromes remain in the research domain [3] [7] [13], highlighting the need for collaborative databases, functional validation frameworks, and multidisciplinary approaches to fully realize the clinical potential of genomic medicine in craniofacial disorders.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

LIMITATIONS

While this scoping review synthesizes valuable insights into genotype–phenotype correlations in rare craniofacial syndromes, several limitations must be acknowledged. First, the possibility of language and publication bias cannot be excluded. Most included studies were published in English-language journals, potentially excluding relevant findings from non-English sources. In addition, case reports and case series that highlight novel or striking associations may be overrepresented, whereas negative or inconclusive findings are less likely to be published, thereby skewing the available evidence.

Second, variability in phenotypic reporting across studies posed challenges in drawing precise genotype–phenotype correlations.
Clinical descriptions ranged from detailed craniofacial measurements and photographic documentation to brief summaries of dysmorphic features, limiting the ability to standardize comparisons. The use of inconsistent terminology across different reports also complicated clustering of features, underscoring the need for harmonized phenotyping frameworks in rare disease research.

Finally, the limited availability of functional data for many rare syndromes restricts the strength of causal inferences. While some variants were supported by in vitro or in vivo validation, others particularly Variants of Uncertain Significance lacked experimental confirmation, making it difficult to definitively establish pathogenicity. This gap highlights the necessity for more integrative studies that combine next-generation sequencing with functional genomics, animal models, and advanced cellular assays.

These limitations suggest that while meaningful trends can be discerned, caution must be exercised in interpreting genotype–phenotype patterns, especially in the context of rare or newly described craniofacial syndromes. Future research that reduces reporting heterogeneity, broadens linguistic and geographic inclusivity, and incorporates functional validation will be critical in strengthening the translational impact of this field.

CONCLUSION

This scoping review provides a comprehensive overview of genotype–phenotype correlations in rare genetic syndromes affecting the head and neck.

The analysis highlighted a wide spectrum of craniofacial and osteodysplastic manifestations, ranging from well-characterized syndromes with established molecular underpinnings to ultra-rare or emerging disorders with incomplete evidence. Syndromes such as Apert, Branchio-oculo-facial, and Axenfeld–Rieger consistently demonstrated distinctive craniofacial signatures, with recurrent pathogenic variants correlating strongly with features such as cleft palate, midface hypoplasia, and micrognathia. In contrast, less common conditions, including Juberg–Hayward syndrome and multilocus osteodysplastic disorders, were primarily reported in isolated cases, emphasizing gaps in functional validation and mechanistic understanding.

The frequent identification of Variants of Uncertain Significance (VUS) across multiple syndromes underscores ongoing challenges in clinical interpretation. While some VUS appeared to cluster with specific phenotypes, functional evidence for most remains limited, highlighting the need for standardized in vitro, in vivo, and computational approaches to assess pathogenicity.
Integration of these functional data with genomic analyses will be crucial for establishing clinically actionable correlations, particularly in syndromes involving transcriptional regulation, splicing fidelity, or key developmental signaling pathways.
Cross-syndrome comparisons revealed that craniofacial anomalies often converge on a limited set of developmental pathways despite underlying genetic heterogeneity. This pattern suggests that disruptions in transcription factors, splicing machinery, or signaling cascades can produce overlapping phenotypes, including cleft palate, mandibular hypoplasia, craniosynostosis, and bone overgrowth. The review also identified important gaps, including insufficient cohort diversity, lack of replication studies, and limited functional validation for rare or newly recognized syndromes.

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.

This article was published on March 31, 2026, at IJPDTM.IT
doi.org/10.30459/2026-2

References

1. Jadico, S.K., Young, D.A., Huebner, A., Edmond, J.C., Pollock, A.N., McDonald-McGinn, D.M., Li, Y.-J., Zackai, E.H. and Young, T.L. (2006). Ocular abnormalities in Apert syndrome: Genotype/phenotype correlations with fibroblast growth factor receptor type 2 mutations. Journal of American Association for Pediatric Ophthalmology and Strabismus, [online] 10(6), pp.521–527. doi:https://doi.org/10.1016/j.jaapos.2006.07.012.
2. Pauws, E., Peskett, E., Boissin, C., Hoshino, A., Mengrelis, K., Carta, E., Abruzzo, M., Lees, M., Moore, G., Erickson, R. and Stanier, P. (2013). Xlinked CHARGE like Abruzzo–Erickson syndrome and classic cleft palate with ankyloglossia result from TBX22 splicing mutations. Clinical Genetics, [online] 83(4), pp.352–358. doi:https://doi.org/10.1111/j.1399-0004.2012.01930.x.
3. Piranit Nik Kantaputra, Prapai Dejkhamron, Worrachet Intachai, Chumpol Ngamphiw, Kawasaki, K., Atsushi Ohazama, Suttichai Krisanaprakornkit, Olsen, B., Sissades Tongsima and Ketudat, J.R. (2020). Juberg-Hayward syndrome is a cohesinopathy, caused by mutation in ESCO2. European Journal of Orthodontics, [online] 43(1), pp.45–50. doi:https://doi.org/10.1093/ejo/cjaa023.
4. Petit, F., F. Escande, Jourdain, A.S., N. Porchet, Amiel, J., Doray, B., M.A. Delrue, Flori, E., Kim, C.A., Marlin, S., Robertson, S.P., S. Manouvrier Hanu and M. Holder Espinasse (2013). Nager syndrome: confirmation of SF3B4 haploinsufficiency as the major cause. Clinical Genetics, [online] 86(3), pp.246–251. doi:https://doi.org/10.1111/cge.12259.
5. Al-Qattan, M.M. and Almohrij, S.A. (2022). The Pathogenesis of Pierre Robin Sequence through a Review of SOX9 and Its Interactions. Plastic & Reconstructive Surgery Global Open, [online] 10(4), pp.e4241–e4241. doi:https://doi.org/10.1097/gox.0000000000004241.
6. Zahra Motahari, Moody, S.A., Maynard, T.M. and LaMantia, A.-S. (2019). In the line-up: deleted genes associated with DiGeorge/22q11.2 deletion syndrome: are they all suspects? Journal of Neurodevelopmental Disorders, [online] 11(1). doi:https://doi.org/10.1186/s11689-019-9267-z.
7. Gogoll, L., Steindl, K., Joset, P., Zweier, M., Baumer, A., Gerth Kahlert, C., Tutschek, B. and Rauch, A. (2021). Confirmation of Ogden syndrome as an X linked recessive fatal disorder due to a recurrent NAA10 variant and review of the literature. American Journal of Medical Genetics Part A, [online] 185(8), pp.2546–2560. doi:https://doi.org/10.1002/ajmg.a.62351.
8. Iovino, E., Luca Scapoli, Palmieri, A., Rossella Sgarzani, Nouri, N., Agnese Pellati, Carinci, F., Seri, M., Tommaso Pippucci and Martinelli, M. (2023). Ultra-Rare Variants Identify Biological Pathways and Candidate Genes in the Pathobiology of Non-Syndromic Cleft Palate Only. Biomolecules, [online] 13(2), pp.236–236. doi:https://doi.org/10.3390/biom13020236.
9. Špela Miroševič, Khandelwal, S., Sušjan, P., Žakelj, N., Gosar, D., Forstnerič, V., Duško Lainšček, Jerala, R. and Damjan Osredkar (2022). Correlation between Phenotype and Genotype in CTNNB1 Syndrome: A Systematic Review of the Literature. International Journal of Molecular Sciences, [online] 23(20), pp.12564–12564. doi:https://doi.org/10.3390/ijms232012564.
10. Miller, S.F., Weinberg, S.M., Nidey, N.L., Defay, D.K., Marazita, M.L., Wehby, G.L. and Moreno, L.M. (2014). Exploratory genotype–phenotype correlations of facial form and asymmetry in unaffected relatives of children with non syndromic cleft lip and/or palate. Journal of Anatomy, [online] 224(6), pp.688–709. doi:https://doi.org/10.1111/joa.12182.
11. Liu, Z., Zhou, D., Wang, C., Zheng, B., Yan, Q., Zhou, W. and Wang, G. (2025). Genetic Insights Into Craniosynostosis: Identification of Novel IL11RA Variants in Chinese Pediatric Patients. Molecular Genetics & Genomic Medicine, [online] 13(5). doi:https://doi.org/10.1002/mgg3.70106.
12. Xu, Y., Zhang, X., Lu, W., Xiao, Y., Ma, X., Chen, L. and Dong, Z. (2025). A novel EFTUD2 splicing variant causing mandibulofacial dysostosis with microcephaly: a case report. Translational Pediatrics, [online] 14(6), pp.1336–1343. doi:https://doi.org/10.21037/tp-2024-587.
13. Christos Yapijakis, Iphigenia Gintoni, Myrsini Chamakioti, Koniari, E., Papanikolaou, E., Kassi, E., Dimitrios Vlachakis and Chrousos, G.P. (2025). Genotype–Phenotype Correlation Insights in a Rare Case Presenting with Multiple Osteodysplastic Syndromes. Genes, [online] 16(8), pp.871–871. doi:https://doi.org/10.3390/genes16080871.
14. Le Goff, C., Michot, C. and Cormier Daire, V. (2014). Myhre syndrome. Clinical Genetics, [online] 85(6), pp.503–513. doi:https://doi.org/10.1111/cge.12365.
15. A. Mitrakos, K. Kekou, F. N. Tilemis, M. Svingou, G. Papadimas, C. Sofocleous, J. Traeger Synodinos and M. Tzetis (2024). Nablus mask like facial syndrome: Report of an atypical case with 8q21.3–q22.1 deletion. American Journal of Medical Genetics Part A, [online] 194(12). doi:https://doi.org/10.1002/ajmg.a.63826.
16. Meshcheryakova, T.I., Zinchenko, R.A., Vasilyeva, T.A., Marakhonov, A.V., Zhylina, S.S., Petrova, N.V., Kozhanova, T.V., Belenikin, M.S., Petrin, A.N. and Mutovin, G.R. (2015). A Clinical and Molecular Analysis of Branchio Oculo Facial Syndrome Patients in Russia Revealed New Mutations in TFAP2A. Annals of Human Genetics, [online] 79(2), pp.148–152. doi:https://doi.org/10.1111/ahg.12098.
17. Sato, T., Samura, O., Kato, N., Taniguchi, K., Takahashi, K., Ito, Y., Aoki, H., Kobayashi, M., Migita, O., Okamoto, A. and Hata, K. (2018). Novel TFAP2A mutation in a Japanese family with Branchio-oculo-facial syndrome. Human Genome Variation, [online] 5(1). doi:https://doi.org/10.1038/s41439-018-0004-z.
18. Luo, F., Lu, M., Zhao, L. and Zhou, P. (2023). A neonatal case report of branchiooculofacial syndrome caused by a novel mutation in the TFAP2A gene and literature review. Medicine, [online] 102(44), p.e34962. doi:https://doi.org/10.1097/md.0000000000034962.
19. Castiglione, A., Melchionda, S., Carella, M., Trevisi, P., Bovo, R., Manara, R. and Martini, A. (2014). EYA1-related disorders: Two clinical cases and a literature review. International Journal of Pediatric Otorhinolaryngology, [online] 78(8), pp.1201–1210. doi:https://doi.org/10.1016/j.ijporl.2014.03.032.
20. Sherlaw-Sturrock, C., Austin, T., Baptista, J., Gilmour, K. and Naik, S. (2022). Dysmorphism and immunodeficiency - One of the differential diagnoses is PAX1 related otofaciocervical syndrome type 2. European Journal of Medical Genetics, [online] 65(7), pp.104523–104523. doi:https://doi.org/10.1016/j.ejmg.2022.104523.
21. Gana, S., Valetto, A., Toschi, B., Sardelli, I., Cappelli, S., Peroni, D. and Bertini, V. (2019). Familial Interstitial 6q23.2 Deletion Including Eya4 Associated With Otofaciocervical Syndrome. Frontiers in Genetics, [online] 10. doi:https://doi.org/10.3389/fgene.2019.00650.
22. Bezerra, J., Oliveira, G., Soares, C., Cardoso, M., MAG Ururahy, Neto, F., LG Lima Neto, AD Luchessi, Silbiger, V., Fajardo, C., Oliveira, S. de, das, M., Hirata, R., Rezende, A. de and Hirata, M. (2014). Genetic and non genetic factors that increase the risk of non syndromic cleft lip and/or palate development. Oral Diseases, [online] 21(3), pp.393–399. doi:https://doi.org/10.1111/odi.12292.
23. Alghonemy, W.Y. and Gaber Ashmawy, M. (2025). Meta-analysis and systematic review for the genetic basis of cleft lip and palate. Journal of Oral Biology and Craniofacial Research, [online] 15(1), pp.146–152. doi:https://doi.org/10.1016/j.jobcr.2024.12.012.
24. Cheng, X., Du, F., Long, X. and Huang, J. (2023). Genetic Inheritance Models of Non-Syndromic Cleft Lip with or without Palate: From Monogenic to Polygenic. Genes, [online] 14(10), p.1859. doi:https://doi.org/10.3390/genes14101859.
25. Miller, S.F., Weinberg, S.M., Nidey, N.L., Defay, D.K., Marazita, M.L., Wehby, G.L. and Moreno Uribe, L.M. (2014). Exploratory genotype–phenotype correlations of facial form and asymmetry in unaffected relatives of children with non syndromic cleft lip and/or palate. Journal of Anatomy, [online] 224(6), pp.688–709. doi:https://doi.org/10.1111/joa.12182.
26. E., C., Ahmed, M., Wang, Y., Wang, J., Wu, S. and Meng, Z. (2025). A Case of Trichorhinophalangeal Syndrome Caused by a Novel Heterozygous Nonsense Mutation in the TRPS1 Gene. Clinical Case Reports, [online] 13(8). doi:https://doi.org/10.1002/ccr3.70695.
27. Herlin, L.K., Herlin, M.K., Blechingberg, J., Rønholt, K., Graversen, L., Schmidt, S.A.J., Jørgensen, M.W., Hellfritzsch, M.B., Hald, J.D., Beck-Nielsen, S.S., Gjørup, H., Andersen, B.N., Gregersen, P.A. and Sommerlund, M. (2024). Clinical presentation and genetics of tricho-rhino-phalangeal syndrome (TRPS) type 1: A single-center case series of 15 patients and seven novel TRPS1 variants. European Journal of Medical Genetics, [online] 69, p.104937. doi:https://doi.org/10.1016/j.ejmg.2024.104937.
28. Nikoletta Selenti, Tzetis, M., Braoudaki, M., Krinio Giannikou, Kitsiou-Tzeli, S. and Fryssira, H. (2015). An interstitial deletion at 8q23.1-q24.12 associated with Langer-Giedion syndrome/ Trichorhinophalangeal syndrome (TRPS) type II and Cornelia de Lange syndrome 4. Molecular Cytogenetics, [online] 8(1). doi:https://doi.org/10.1186/s13039-015-0169-9.
29. Zhang, Y., Chen, X., Wang, L., Sun, X. and Chen, Y. (2021). Heterogeneity of Axenfeld–Rieger Syndrome: Molecular and Clinical Findings in Chinese Patients. Frontiers in Genetics, [online] 12. doi:https://doi.org/10.3389/fgene.2021.732170.
30. Gong, X., Lei, X., Li, Z. and Xing, Y. (2025). Identification and functional study of a novel FOXC1 missense mutation in a Chinese family with Axenfeld–Rieger syndrome. Scientific Reports, [online] 15(1). doi:https://doi.org/10.1038/s41598-025-04872-x.
31. White, S., Taranath, A., Hanagandi, P., Taranath, D.A., To, M.-S., Souzeau, E., Siggs, O.M. and Craig, J.E. (2023). Neuroimaging Findings in Axenfeld-Rieger Syndrome: A Case Series. AJNR. American journal of neuroradiology, [online] 44(10), pp.1231–1235. doi:https://doi.org/10.3174/ajnr.A7995.
32. Zhou, L., Wang, X., An, J., Zhang, Y., He, M. and Tang, L. (2022). Genotype-phenotype association of PITX2 and FOXC1 in Axenfeld-Rieger syndrome. Experimental Eye Research, [online] 226, pp.109307–109307. doi:https://doi.org/10.1016/j.exer.2022.109307.
33. Keppler-Noreuil, K.M., Martinez-Agosto, J.A., Hudgins, L. and Carey, J.C. (2017). 37th Annual David W. Smith Workshop on Malformations and Morphogenesis: Abstracts of the 2016 Annual Meeting. American Journal of Medical Genetics Part A, [online] 173(8), pp.2007–2073. doi:https://doi.org/10.1002/ajmg.a.38229.
34. French, C. R. (2021). Mechanistic Insights into Axenfeld–Rieger Syndrome from Zebrafish foxc1 and pitx2 Mutants. International Journal of Molecular Sciences, 22(18), 10001–10001. https://doi.org/10.3390/ijms221810001
35. Yang, D., Jian, Z., Tang, C., Chen, Z., Zhou, Z., Zheng, L. and Peng, X. (2024). Zebrafish Congenital Heart Disease Models: Opportunities and Challenges. International Journal of Molecular Sciences, [online] 25(11), pp.5943–5943. doi:https://doi.org/10.3390/ijms25115943.
36. Jbi.global. (2024). Revised JBI Methodology for Systematic Reviews of Textual Evidence | JBI. [online] Available at: https://jbi.global/news/article/revised-jbi-methodology-systematic-reviews-textual-evidence [Accessed 18 Nov. 2025].

Publisher's note: *all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers.*
Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.
©Copyright: the Author(s), 2026

This work is licensed under a Creative Commons Attribution 4.0 License (by-nc 4.0).
Simedet.