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Review

Molecular Basis of Variations in Facial Soft Tissues: Insights from Cichlids

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Abstract

The human face serves as a crucial component of attractiveness and identity, playing a pivotal role in social interactions. The genetic legacy of the human face reaches back to the evolution of the vertebrate jaw, via transformation of the third gill-arch of lamprey-like ancestors. Teleost fish models, particularly zebrafish, have offered valuable insights into the developmental and molecular mechanisms governing craniofacial skeletogenesis, owing to the molecular conservation in these processes. However, knowledge regarding the morphogenic processes shaping facial soft tissues remains surprisingly sparse. The diverse family of Cichlidae constitute ~10% of teleost fish species and represent an exceptional opportunity for evolutionary biology research due to their extensive ecological diversity and rapid speciation rates. Cichlid fishes also exhibit remarkable craniofacial morphological diversity, making them excellent models for studying both craniofacial skeletal and soft tissue morphogenesis. Utilizing the wealth of natural mutants within cichlid populations, this short review pitches cichlid fish models as valuable tools for investigating the genetic regulators and interactions underlying facial soft tissue formation. By synthesising developmental and regulatory mechanisms that influence morphological variations in facial soft tissues in cichlids and other model organisms, we create a blueprint for forthcoming molecular genetic investigations into facial diversity across various species and facial deformities in humans.

Keywords: craniofacial development; facial soft tissues; Gene regulation; cichlids; morphological diversity

Introduction

In recent years, the investigation of how facial soft tissues develop has gained significant attention due to its implications for human health and overall well-being (Chaimongkhol and Mahakkanukrauh, 2022; Cotofana and Lachman, 2019; Giri et al., 2024; Hersberger-Zurfluh et al., 2018; Hînganu et al., 2024; Qian et al., 2022; Richmond et al., 2018; Weber et al., 2021). The face holds a central position in both attractiveness and identity, crucial for shaping interpersonal interactions among humans. Any abnormalities in facial appearance, whether present from birth or acquired later, can profoundly affect an individual's quality of life, often resulting in social stigma and negative emotional consequences due to perceived deviations from societal norms (Bull and Rumsey, 1988; Little et al., 2011; Samson et al., 2010). Furthermore, society's increasing focus on facial aesthetics underscores the importance of focusing on the complex molecular processes involved in the formation of facial soft tissues.

Facial soft tissues make significant contributions to a complex array of structures, including the lips, nose, ears, cheeks, chin, and forehead, each with distinct structural and functional characteristics

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(Nanda et al., 1990). The formation of these tissues involves complex molecular pathways that regulate cellular differentiation, proliferation, and patterning (Landi et al., 2022; Quinto-Sánchez et al., 2018; Szabo-Rogers et al., 2008; Weber et al., 2021). Despite the unique importance of facial soft tissues, our understanding of the molecular processes governing their morphogenesis, and how these contribute to overall facial geometry, remains limited. For example, genetic association studies in humans have implicated various genetic factors in shaping facial soft tissues structures (Naqvi et al., 2022). Other studies have shown that the morphology of specific parts of the human face, such as the forehead, upper lips, and nose, exhibit high heritability, offering these anatomical regions as prime candidates for exploring the genetic contributions to facial soft tissue variation (Giri et al., 2024; Hersberger-Zurfluh et al., 2018; Jelenkovic et al., 2010; Qian et al., 2022; Richmond et al., 2018; Song et al., 2018). However, further functional and developmental investigations are needed to dissect the molecular mechanisms through which they operate. Traditional mammalian models for genetic studies have provided valuable insights into various biological processes, including craniofacial development. But ethical considerations and practical constraints limit the feasibility of conducting extensive genetic manipulations and experimental studies in mammalian models (Higashiyama et al., 2025; Xie et al., 2024). Furthermore, the long gestation period and relatively low reproductive rates of mammalian models can impede the pace of research and limit the scope of studies investigating the molecular mechanisms underlying facial soft tissue morphogenesis. On the other hand, teleost fish models, such as zebrafish, although instrumental in elucidating the developmental and molecular mechanisms governing craniofacial skeletogenesis, lack pronounced facial soft tissue structures comparable to mammals (Ibarra and Atit, 2020).

In contrast to zebrafish, the naturally diverse family of Cichlidae emerges as model for investigating morphological variation in facial soft tissues. Cichlid fishes exhibit remarkable craniofacial morphological diversity (Conith and Albertson, 2021; Cooper et al., 2010; Fryer and Iles, 1972; Liem, 1973; Powder et al., 2015, 2014; Powder and Albertson, 2016), with exaggerated facial soft tissues and complex facial structures (Colombo et al., 2013; Concannon and Albertson, 2015; Conith et al., 2019, 2018; Duenser et al., 2023; Henning et al., 2017; Lecaudey et al., 2021, 2019; Machado-Schiaffino et al., 2017; Machii et al., 2025; Rometsch et al., 2021). Notably, the extensive diversity among cichlids has evolved in the context of gene flow and overall low levels of genetic divergence, making this system ideal for genetic/association mapping (Albertson et al., 2003; Brawand et al., 2014; Carmona Baez et al., 2025; Hulsey et al., 2017; Kautt et al., 2020; Parnell et al., 2012; Santos et al., 2023; Torres-Dowdall and Meyer, 2021). Furthermore, the availability of high quality annotated genomic data from diverse but phylogenetically closely related species of cichlids, coupled with established genetic manipulation tools like CRISPR/Cas9 (Clark et al., 2023; Marconi et al., 2024; Santos et al., 2014), positions cichlid fishes as powerful models for studying the genetic regulators and interactions underlying facial soft tissue formation. The wealth of natural mutants among cichlids and their experimental tractability make them amenable to elucidate the molecular pathways shaping facial soft tissues and their role in morphological variation.

This review provides a concise overview of recent molecular findings in cichlids related to facial soft tissue morphogenesis (excluding muscles and tendons). By connecting these findings to previous research in humans and other species, we seek to establish cichlid fish models as valuable tools for investigating facial diversity across various species and for decoding its underlying genetic regulatory networks. Overall, this review highlights the timeliness and significance of utilizing cichlid fish models in advancing our understanding of facial soft tissue morphogenesis and its implications for human health.

Facial Soft Tissues

In recent decades, craniofacial genetic research has transitioned from primarily focusing on anomalies to understanding the biological basis of normal facial variation. This expanded focus is aided by advancements in high-resolution three-dimensional systems for precise facial feature capture and sequencing technology for exploring genetic impacts on facial characteristics (Richmond

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et al., 2018). Investigating the genetics of normal-range facial morphology is essential for several reasons. Firstly, it elucidates the interplay between environmental factors and parental biological contributions, revealing the origins of individual appearance. Secondly, in certain instances specific but subclinical craniofacial shape in parents can indicate an elevated risk of dysmorphology in children (El Sergani et al., 2021). Furthermore, genetic data can determine ancestry, sex, and specific facial features, with applications in healthcare and forensics. Finally, studying historical selection and adaptation informs craniofacial evolution research, while exploring shared facial traits, medical conditions, and genes offers insights into commonalities and differences among individuals (Richmond et al., 2018).

Most craniofacial tissues originate from cranial neural crest cells (CNCCs), which undergo epithelial-to-mesenchymal transition and migrate ventrally to form most of the craniofacial skeleton and connective tissue (Som and Naidich, 2013). During early embryonic development, CNCCs divide into frontonasal and pharyngeal arches, with the frontonasal prominence giving rise to the forehead and nasal bones (Cordero et al., 2011). Subsequently, nasal placodes develop into lateral and medial nasal prominences, while mandibular prominences merge to form the mandible. Fusion of nasal and maxillary prominences leads to the formation of central nose structures (Cordero et al., 2011; Som and Naidich, 2013). Finally, fusion of remaining facial structures occurs, with subsequent growth and maturation throughout the embryogenesis. The development facial soft tissues also involve complex embryonic processes closely linked to CNCCs (Richmond et al., 2018). In mammals, facial soft tissue development comprises distinct components, including frontonasal (forehead and upper eyelid), medial nasal (nose and upper lip/philtrum), lateral nasal (sidewalls of the nostrils and base of the nose), maxillary (lower eyelids, cheeks and lateral parts of the upper lip), and mandibular (the entire lower lip) regions, which fuse at different stages of embryonic development (Richmond et al., 2018). Molecular studies highlight the complex interactions of various factors and pathways, such as fibroblast growth factors, hedgehog proteins, bone morphogenetic proteins, Wnt signaling, retinoic acid signaling, homeobox genes, etc., in regulating facial primordia growth and patterning (Ahi, 2016; Richmond et al., 2018). Disruptions in facial process fusion can lead to facial, lip, or palate clefts. In human, the postnatal facial growth follows general somatic growth patterns, with distinct periods of steady and rapid growth, peaking at puberty (Som and Naidich, 2013). The timing, direction, and duration of growth surges vary between genders and populations, contributing to overall facial variation (Matthews et al., 2018).

Facial variation is a consequence of genetic and environmental factors (Naqvi et al., 2022). Genetic influences are evident through familial resemblance and similarities between monozygotic twins compared to dizygotic twins (Giri et al., 2024; Hersberger-Zurfluh et al., 2018). Shared facial characteristics within ancestries and sexes, as well as distinctive features associated with genetic conditions, further illustrate genetic influence on facial appearance. Studies estimating facial heritability traditionally involve comparing facial similarity among relatives like twins or parents and offspring. With advancements in technology, large-scale analyses using genome-wide association study (GWAS) have become feasible (Finucane et al., 2015), even in cichlid fishes (Singh et al., 2025). Strong genetic influences, particularly on upper and midfacial regions (e.g. forehead, upper lip and nose) (Figure 1A), have been consistently reported (Hoskens et al., 2018; Tsagkrasoulis et al., 2017), whereas stronger environmental contributions observed in the lower parts of the face (e.g. lower lip, mandibular regions and chin) (Naqvi et al., 2022). Environmental influences such as nutrition, aging, oral function, prenatal exposure to teratogens, and climatic factors also contribute to facial shape variation.

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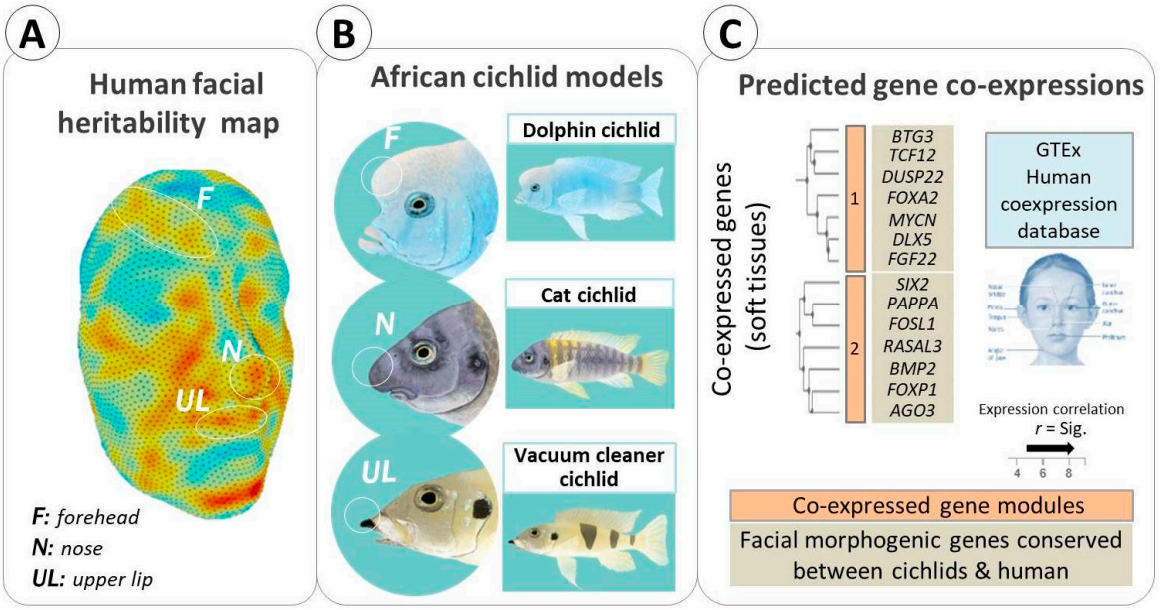

Figure 1. Examples of cichlid fish models for studying the heritable morphologies of human face. (A) Heritability map of human face. Red and blue areas indicate high and low levels of heritability, respectively (www.heritabilitymaps.info). **(B)** African cichlids as models to study facial areas with high of levels of heritability in human (e.g. forehead, nose and upper lip). **(C)** Examples of predicted co-expression of facial morphogenic genes in human soft tissues (www.gtexportal.org) with potentially conserved role in cichlids.

Cichlid Diversity in Facial Morphology Beyond Skeletal Tissues

Cichlid fishes, particularly those from East African lakes, are renowned for their exceptional craniofacial diversity (Santos et al., 2023), making them a prime model for studying the genetic and developmental mechanisms underlying craniofacial variation (Powder and Albertson, 2016). This diversity encompasses a wide array of jaw structures, skull shapes, and facial soft tissues, each adapted to specific ecological niches and feeding strategies. While much research has focused on craniofacial skeletogenesis (Albertson and Kocher, 2006; Roberts et al., 2011, Singh et al 2017, WGCNA paper 2021, Ahi et al 3-lake qPCR paper), more recent studies have begun to explore the diversity in facial soft tissues, providing new insights into the evolutionary biology of these species (Concannon and Albertson, 2015; Conith et al., 2019, 2018; Duenser et al., 2023; Henning et al., 2017; Lecaudey et al., 2021, 2019). Historically, research has predominantly focused on the bony components of cichlid craniofacial anatomy. Studies have elucidated how variations in jaw morphology and skull structure contribute to the exploitation of diverse trophic resources (Fraser et al., 2009; Powder and Albertson, 2016). For instance, differences in jaw shape and kinematics and dental arrangements have been linked to specific feeding habits, such as algae scraping or mollusk crushing (Ahi et al., 2019; Fraser et al., 2009; Hu and Albertson, 2014; Singh et al., 2021). These skeletal adaptations are often governed by conserved molecular pathways, including Wnt and Hedgehog signaling, which modulate bone development and morphogenesis (Navon et al., 2020; Parsons et al., 2014; Roberts et al., 2011); however, novel genes have also been implicated (Powder et al., 2014; Gilbert et al., 2021), which underscores the potential of the cichlid system to reveal new molecular mechanisms into the regulation of craniofacial shape.

While skeletal structures have been extensively studied, there has been a burgeoning interest in the diversity of craniofacial soft tissues among cichlids. Soft tissue features, such as hypertrophied lips, forehead/nuchal humps, and nasal protrusions, play significant roles in feeding strategies, mate attraction, and species recognition (Baumgarten et al., 2015; Concannon and Albertson, 2015; Conith et al., 2019; Darrin Hulsey et al., 2018; Duenser et al., 2023; Henning et al., 2017; Lecaudey et al., 2021, 2019). These traits often evolve rapidly and can exhibit remarkable variability even among closely

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related species. Recent transcriptomic analyses have begun to uncover the molecular underpinnings of these soft tissue adaptations (Duenser et al., 2023; Lecaudey et al., 2021, 2019). For example, studies on species with pronounced lip hypertrophy have identified differential expression of genes involved in cell proliferation, extracellular matrix formation, and lipid metabolism (Henning et al., 2017; Lecaudey et al., 2021). Similarly, research into the development of nuchal humps, a prominent forehead swelling observed in certain cichlid species, has revealed the involvement of genes regulating adipogenesis, cell growth, and craniofacial morphogenesis (Lecaudey et al., 2019). These findings suggest that modifications in gene expression and signaling pathways contribute to the evolution of soft tissue diversity in cichlid fishes. Examples of soft tissue diversification in cichlids that are studied at molecular level are:

Hypertrophied Lips: In species such as *Gnathochromis permaxillaris* (so-called vacuum cleaner cichlid), exaggerated lip structures have evolved, potentially enhancing their ability to forage by creating a more effective seal against substrates. Transcriptomic studies have identified upregulation of genes associated with tissue remodeling and structural integrity in these species (Lecaudey et al., 2021). A recent comprehensive study assessed the convergent transcriptional changes underlying hypertrophied lips across the three Great Lakes of Africa, using *Haplochromis chilotes*, *Placidochromis milomo*, and *Lobochilotes labiatus* as models. Interestingly, they found a conserved set of overlapping ECM remodeling genes at the core of these repeated phenotypes (Machii et al., 2025).

Nuchal Humps: The dolphin cichlid (*Cyrtocara moorii*) from Lake Malawi in Eastern Africa exhibits a prominent nuchal hump (in forehead region), which may serve as a visual signal in social interactions or play a role in fat storage. Gene expression profiling of the nuchal hump tissue has highlighted the activation of pathways related to cell proliferation and differentiation (Lecaudey et al., 2019), indicating a complex regulatory network governing this trait.

Nasal Protrusions: Certain cichlid species from Lakes Tanganyika and Malawi, so called cat cichlids, display hypertrophied nasal structures, which are thought to be involved in either enhanced foraging efficiency or sexual selection. Investigations into these features have revealed the involvement of conserved cell, tissue and molecular players also implicated in human facial development, underscoring the relevance of cichlid models in understanding vertebrate facial diversity (Concannon and Albertson, 2015; Conith et al., 2019, 2018; Duenser et al., 2023).

In short, the rapid diversification of craniofacial traits in cichlids, driven by ecological pressures and sexual selection, offers insights into how genetic and environmental factors can interplay to produce phenotypic variation. Moreover, the molecular players identified during the morphogenesis of cichlid facial soft appear to be conserved across vertebrates (see examples in Figure 1), making these fishes pertinent models for understanding human craniofacial development, dysmorphology and diseases.

Examples of Conserved Genes Underlying Facial Soft Tissue Morphogenesis

Facial soft tissue morphogenesis is shaped by conserved genetic pathways that regulate mesenchymal proliferation, ECM remodeling, and epithelial-mesenchymal interactions. Many key genes involved in human and mouse craniofacial development also play roles in cichlid facial soft tissue formation. This section highlights a handful of example genes with known functions in mammalian facial development that have also been identified in cichlids with distinct nasal, forehead and lip hypertrophy. While not exhaustive, these examples illustrate the molecular parallels between cichlids and mammals, reinforcing their value as a model for studying vertebrate facial soft tissue evolution and morphogenesis (Figure 2).

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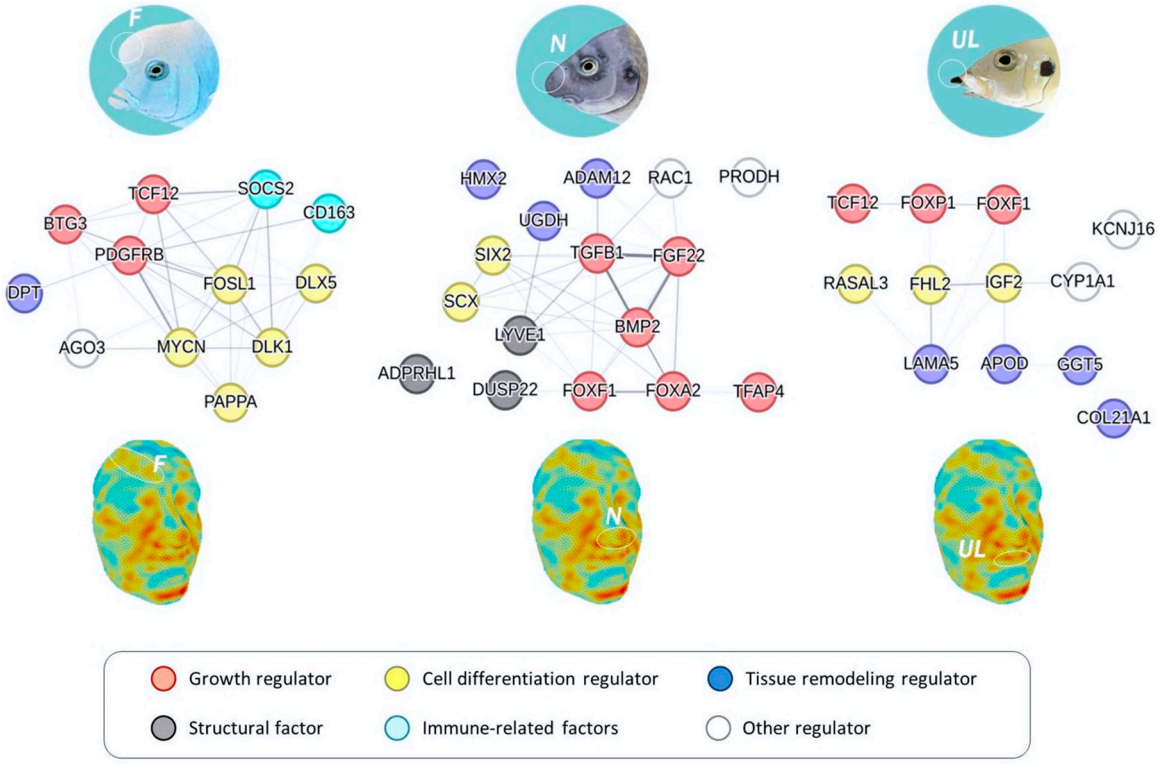

Figure 2. Interactome maps of conserved genes involved in facial soft tissue morphogenesis in cichlid fish models and humans. Regulatory interactions among candidate genes identified as drivers of morphological changes in the forehead, nasal regions, and upper lip of selected cichlid models (with potentially similar roles in humans) are shown using the STRING database. The interactions are based on available knowledge of protein–protein associations, transcriptional regulatory connection, and biochemical interactions.

Growth regulators: Growth factor signals play a central role in facial soft tissue morphogenesis, directing mesenchymal proliferation, differentiation, and extracellular matrix (ECM) remodeling. In cichlid fish, these pathways contribute to three key facial modifications, nasal, forehead (nuchal hump), and lip hypertrophy, through a conserved set of genetic regulators. The genes *amad12*, *tgf-β1*, *fgf22*, *foxf1*, *foxa2*, *bmp2*, and *tfap4* drive nasal protrusion development (Conith et al., 2018; Duenser et al., 2023), while *pdgfrb*, *btg3*, and *tcf12* regulate forehead hypertrophy (Lecaudey et al., 2019). Meanwhile, *foxp1*, *tcf12*, and *foxf1* contribute to lip hypertrophy (Lecaudey et al., 2021). The shared features among these three morphogenetic processes likely reflect a conserved role in driving similar tissue-level outcomes, particularly the hypertrophy of facial soft tissues.

In human, *TGF-β1*, *BMP2*, *FGF22*, and *TFAP4* play critical roles in epithelial-mesenchymal interactions and mesenchymal proliferation, facilitating expansion of nasal soft tissues (Gupta et al., 2020). *TGF-β1*, a key regulator of tissue remodeling and fibroblast activation, has been linked to nasal tissue expansion in cichlids, similar to its role in human craniofacial development (Gupta et al., 2020). *BMP2*, a fundamental driver of soft tissue morphogenesis, influences cell fate and ECM production, reinforcing nasal mesenchymal structure (Tan et al., 2017). *FGF22*, involved in epidermal homeostasis and tissue repair, contributes to the regulation of epithelial integrity during nasal expansion (Quigley et al., 2004). *FOXA2* and *FOXF1*, transcription factors crucial for mesodermal and endodermal tissue specification, have been identified in nasal mesenchyme, where they modulate mesenchymal-epithelial signaling, further supporting their role in soft tissue patterning across vertebrates (Dines et al., 2019; Kucharczyk et al., 2014). *TFAP4*, a transcription factor regulating cell proliferation and differentiation, has been implicated in as potential upstream regulator of gene networks involved in epithelial thickening in nasal protrusions (Gervasini et al., 2007), which is also a feature of nasal expansion in cichlid species (Conith et al., 2019).

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For forehead hypertrophy (nuchal hump formation), *pdgfrb, btg3* and *tcf12* regulate fibroblast proliferation, mesenchymal expansion, and connective tissue remodeling (Lecaudey et al., 2019). *Pdgfrb* (Platelet-Derived Growth Factor Receptor Beta) is a major player in connective tissue expansion and fibroblast proliferation, and its expression is significantly upregulated in cichlids with pronounced forehead structures (Lecaudey et al., 2019), mirroring its role in mammalian craniofacial soft tissue development (Bredrup et al., 2018; Fantauzzo and Soriano, 2016; McCarthy et al., 2016; Saultz et al., 2016; Takenouchi et al., 2015). In human, *BTG3*, a cell cycle regulator, modulates mesenchymal proliferation, ensuring controlled facial soft tissue thickening (Errichiello et al., 2016). In mammals, *TCF12*, a transcription factor essential for tissue differentiation and patterning, contributes to species-specific variation in forehead structure, demonstrating its conserved function in soft tissue morphogenesis (Le Tanno et al., 2014; Piard et al., 2015; Sharma et al., 2013).

In the upper lip specific hypertrophy, *foxp1, tcf12* and *foxf1* are implicated play role in epithelial thickening, mesenchymal expansion, and fibroblast differentiation (Lecaudey et al., 2021). FOXP1 and FOXF1, both involved in mesenchymal-epithelial interactions, are suggested to play roles in fibroblast differentiation and ECM organization in cichlid lips, most likely mirroring their function in human craniofacial soft tissue development (Meerschaut et al., 2017; Shaw-Smith, 2010; Xu et al., 2016). TCF12, also found in forehead hypertrophy, is suggested to contribute to tissue remodeling and connective tissue specialization in the upper lip region, reinforcing its widespread role in facial soft tissue variation (Piard et al., 2015). The recurrent use of TCF12 and FOXF1 in multiple regions suggests that growth factor signaling is modular and adaptable, allowing for diverse morphological outcomes across species. This highlights cichlids as an effective model system for investigating the molecular basis of facial soft tissue development and variation in vertebrates, including humans.

Regulators of cell differentiation: Cell differentiation is a fundamental process in facial soft tissue morphogenesis, directing the specialization of fibroblasts, mesenchymal cells, and epithelial cells across different facial regions. In cichlid fish, conserved regulatory genes have been identified in nasal protrusions, forehead hypertrophy, and lip hypertrophy, playing key roles in tissue-specific differentiation. Among these, *scx* (Scleraxis) and *six2* are implicated in nasal protrusion development, particularly in modulating ligamentous tissues, connective tissue and mesenchymal cell specification (Conith et al., 2018; Duenser et al., 2023). *Scx*, a well-known transcription factor regulating tendon and ligament differentiation, has been implicated in the structural integrity of nasal mesenchyme (Sugimoto et al., 2013), ensuring proper tissue remodeling and flexibility in species with elongated nasal protrusions (Conith et al., 2018). Similarly, *six2*, which plays a major role in craniofacial mesenchymal stem cell regulation, is crucial for proliferation and fate determination in nasal soft tissues (Hufnagel et al., 2016; Okello et al., 2017), supporting its role in vertebrate facial morphogenesis.

In forehead hypertrophy (nuchal hump formation), genes such as *dlk1, papp-a, dlx5a, fosl1a,* and *mycn* regulate mesenchymal differentiation, connective tissue expansion, and adipogenesis (Lecaudey et al., 2019). *Dlk1* (Delta-Like 1 Homolog), a well-known Notch signaling modulator, functions as an inhibitor of adipocyte differentiation, potentially influencing fat accumulation patterns in the nuchal hump, and in mammals is also involved in facial soft tissue morphogenesis (Abdallah et al., 2011; Begemann et al., 2012). In contrast, *Papp-a* (Pregnancy-Associated Plasma Protein-A) enhances IGF signaling, promoting mesenchymal growth and expansion in the forehead region, as shown in mice (Conover et al., 2004). Dlx5, a transcription factor with conserved role in morphogenesis of various craniofacial soft tissue (Chung et al., 2010; Holleville et al., 2003; Talbot et al., 2010; Vera-Carbonell et al., 2012), is also upregulated in cichlids with prominent forehead structures. In human, *FOSL1A*, part of the Ap-1 transcription factor complex, is linked to connective tissue patterning (Mirzamohammadi et al., 2018; Van Mater et al., 2013; Yu et al., 2018), while *MYCN*, a key cell cycle regulator, drives mesenchymal cell proliferation (Mirzamohammadi et al., 2018; Van Mater et al., 2013; Yu et al., 2018), supporting its proposed role in formation of the nuchal hump morphology.

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For the upper lip specific hypertrophy, *rasal3*, *fhl2* and *igf2* regulate fibroblast differentiation, epithelial remodeling, and mesenchymal expansion (Lecaudey et al., 2021). RASAL3, a Ras-GTPase activator, modulates fibroblast signaling, ensuring balanced lip tissue differentiation and proliferation (Draaken et al., 2013; Kosaki et al., 2011). FHL2, a LIM-domain protein, integrates mechanical and biochemical signals to regulate muscle and connective tissue adaptation, potentially influencing lip thickness and elasticity in hypertrophied cichlid lips (Labalette et al., 2008; Manousaki et al., 2013; Ng et al., 2011). IGF2 (Insulin-like Growth Factor 2), a key driver of tissue growth and differentiation, is upregulated in cichlids with exaggerated lips, where it likely promotes mesenchymal proliferation and ECM remodeling (Peñaherrera et al., 2010). Together, these differentiation regulators illustrate the molecular conservation of facial soft tissue morphogenesis, emphasizing the functional parallels between cichlid and mammalian craniofacial development.

Modulators of tissue remodeling: The morphogenesis of facial soft tissues relies not only on structural ECM components but also critically on modulators that guide tissue remodeling, including matrix turnover, cellular behavior, and microenvironmental signaling. These modulators orchestrate dynamic ECM remodeling processes that shape the face during development and evolution. In cichlid fishes, several genes with conserved roles in human craniofacial morphogenesis have been identified as key players in region-specific hypertrophic phenotypes, particularly in the nasal protrusion, forehead, and lip regions. Their functional convergence across these domains highlights the modular yet integrated nature of facial soft tissue evolution.

In the context of nasal protrusion development, three modulator genes; *adam12*, *ugdh*, and *hmx2*, have been shown to exhibit coordinated expression and function (Duenser et al., 2023). ADAM12, a metalloprotease-disintegrin, is known to influence ECM remodeling by modulating cell-matrix interactions and activating latent growth factors such as TGF-β (Ruff et al., 2015), which are crucial for mesenchymal proliferation and migration. Its involvement in nasal protrusion formation in cichlids mirrors its known role in midfacial growth in mammals (Conith et al., 2018; Feng et al., 2009). UGDH (UDP-glucose 6-dehydrogenase), by catalyzing the production of glycosaminoglycan precursors such as hyaluronic acid, plays a central role in regulating ECM hydration and compressibility, factors essential for soft tissue expansion and morphogenesis (Alhamoudi et al., 2020). HMX2, a transcription factor, modulates gene networks involved in facial development and has been associated with nasal and midfacial prominence shaping in vertebrates (Miller et al., 2009). Together, these three genes likely form a regulatory module that facilitates nasal protrusion via localized ECM remodeling and cellular proliferation.

A similar tissue remodeling theme underlies the exaggerated soft tissue phenotype observed in the forehead region, particularly in species exhibiting nuchal humps (Lecaudey et al., 2019). Dermatopontin (*dpt*), a small ECM protein with known roles in collagen fibrillogenesis and tissue organization, is markedly upregulated in species with this trait. In mammals, DPT is involved in skin matrix integrity and dermal fibroblast function (Krishnaswamy et al., 2017; Krishnaswamy and Korrapati, 2015; Liu et al., 2013), and its upregulation in cichlid forehead tissues suggests a role in maintaining the tensile and structural properties of the expanded connective tissue mass. Unlike purely structural ECM components, DPT interacts dynamically with other matrix molecules, modifying the extracellular environment to support prolonged soft tissue hypertrophy.

The upper lip region provides another example of how tissue remodeling modulators contribute to localized facial outgrowths. Genes such as *lama5*, *apoda*, *ggt5a*, and *col21a1* act in synergy to drive lip hypertrophy (Lecaudey et al., 2021; Masonick et al., 2023). LAMA5, a laminin subunit, contributes to the basement membrane and mediates epithelial–mesenchymal interactions crucial for lip tissue adhesion and outgrowth (Peixoto da-Silva et al., 2012). Apoda, a member of the apolipoprotein family, has putative roles in lipid transport and may contribute to the metabolic support of growing soft tissues (Dassati et al., 2014; Manousaki et al., 2013). GGT5A (gamma-glutamyltransferase 5) participates in redox balance and amino acid metabolism, potentially influencing cellular proliferation within remodeling regions (Pinchefsky et al., 2017). Meanwhile, COL21A1, a FACIT collagen, modulates the interaction of fibrillar collagens with surrounding ECM components and

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plays a more regulatory than structural role in maintaining ECM architecture (Mohamad Shah et al., 2019). These genes collectively modulate the microenvironment of the lip region, promoting region-specific hypertrophy via ECM remodeling and enhanced tissue plasticity.

Most strikingly, a conserved module of ECM regulator genes; decorin (*dcn*), lumican (*lum*), and asporin (*aspn*), has been recently implicated in the hypertrophy of the entire lips (both upper and lower), a trait observed repeatedly and independently across the three Great African Lakes (Victoria, Malawi, and Tanganyika) (Machii et al., 2025). These genes encode small leucine-rich proteoglycans (SLRPs) that modulate collagen fibrillogenesis, matrix organization, and tissue elasticity. In mammals, these SLRPs are essential for soft connective tissue integrity and remodeling, particularly in skin and cartilage (Pang et al., 2020). Their shared upregulation in cichlids with hypertrophied lips suggests that these genes orchestrate a conserved remodeling program capable of generating robust, convergent phenotypes (Machii et al., 2025). Their repeated recruitment across evolutionary lineages supports a model where modular ECM remodeling pathways are co-opted to drive parallel facial adaptations in distinct ecological and phylogenetic contexts. Thus, *dcn*, *lum*, and *aspn* exemplify how conserved genetic pathways can underpin repeated morphogenetic outcomes across species.

Structural factors: Structural genes encoding core ECM components and scaffolding proteins support facial morphology by providing biomechanical structure and regulating signaling pathways. In cichlid fishes, which show diverse facial soft tissue forms, regionally expressed structural genes are linked to distinct hypertrophic traits. These patterns are consistent with their roles in vertebrate craniofacial development and suggest relevance to human facial morphogenesis.

In the context of nasal protrusion, three structural genes, *adprhl1*, *dusp22*, and *lyve1*, have emerged as potential important players (Duenser et al., 2023). ADPRHL1 encodes a muscle-specific, actin-associated protein related to the ADP-ribosylation family. While it has been most studied in cardiac and skeletal muscle contexts, its association with tissue scaffolding and actin cytoskeleton remodeling suggests a structural role in shaping the soft nasal tissue matrix during protrusion (De Pater et al., 2005). DUSP22, though primarily known as a dual-specificity phosphatase, has emerging links to cytoskeletal dynamics and tissue architecture, potentially acting through regulation of cell-matrix interactions (Hosono et al., 2020). LYVE1, a lymphatic vessel endothelial hyaluronan receptor, is an ECM-interacting protein implicated in hyaluronan transport and matrix hydration (Mitteldorf et al., 2018). Its expression in nasal protrusion zones of cichlids suggests it contributes to the viscoelastic properties and expansion potential of this soft tissue region, echoing its role in mucosal tissues in mammals.

The most extensive array of structural ECM genes is associated with the whole-lip hypertrophy phenotype observed in multiple cichlid lineages across the African Great Lakes. This striking convergence has been underpinned by upregulation of collagen type I alpha chains (*col1a1a*, *col1a1b*, *col1a2*), fibrillar collagens that provide tensile strength and form the backbone of connective tissues (Machii et al., 2025). These genes are fundamental in maintaining dermal structure and are conserved components in vertebrate skin and oral tissue (Arseni et al., 2018; Lim et al., 2020). Their repeated involvement in lip thickening across lakes highlights their evolutionary utility in reinforcing expanded soft tissues. Accompanying the collagen framework are elastin microfibril interface-located proteins (*emilin1b*, *emilin2a*, *emilin2b*, *emilin3b*), which regulate elastogenesis and microfibril formation (Machii et al., 2025). These proteins not only maintain elasticity and structural resilience in soft tissues like lips but also influence TGF-β signaling, linking them to morphogenetic regulation. In humans, EMILIN family members are expressed in elastic connective tissues such as the dermis and oral mucosa, suggesting deep conservation of their function in lip flexibility and expansion (Fitoussi et al., 2019; Schiavinato et al., 2024).

Further supporting this ECM complex are hyaluronan and proteoglycan link proteins (*hapln1a/b*, *hapln3*) and versican (*vcanb*), which stabilize the hyaluronan-based matrix and confer compressibility and hydration to soft tissues. These genes contribute to matrix swelling and pliability, crucial properties in the hypertrophied lips of many cichlid species (Machii et al., 2025). Similarly, periostin (*postna/b*), an ECM glycoprotein known for its role in collagen cross-linking and tissue remodeling, is

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enriched in cichlid lip tissues and is recognized in mammals for its involvement in periodontal ligament and skin ECM maintenance (Machii et al., 2025). Collectively, these genes form a robust structural gene network that underlies the convergent evolution of full-lip hypertrophy in geographically and phylogenetically distinct cichlid lineages.

Finally, some other structural contributors like *cldn7* and *actb* involved in ECM remodeling may also play supportive role (Colombo et al., 2013). CLDN7 (claudin 7), a tight junction protein, helps maintain epithelial integrity and may influence localized adhesion and barrier properties at the lip margin. ACTB (beta-actin), while broadly expressed, contributes to cytoskeletal tension and interacts with ECM structures during tissue expansion. Though not ECM in the classical sense, these proteins support the structural integrity of soft tissue outgrowths and interact closely with matrix components.

Other potential molecular players: Beyond structural and remodeling genes, other molecular players, such as ion transporters, and immune regulators, support facial soft tissue morphogenesis by coordinating signaling and tissue homeostasis. In cichlids, their region-specific expression suggests roles in traits like nasal protrusion, nuchal humps, and lip hypertrophy, offering insights into conserved regulatory mechanisms across vertebrates.

Among mediators of cell communication and ion transporters, several genes have been associated with distinct facial regions. In nasal protrusion, *prodh* and *rac1* stand out (Duenser et al., 2023). PRODH (proline dehydrogenase) is involved in proline metabolism and influences redox signaling, which can affect cell proliferation and tissue remodeling during craniofacial development (Guilmatre et al., 2010). RAC1, a small GTPase, regulates actin cytoskeletal dynamics, cell adhesion, and migration, functions that are critical for shaping the protruding nasal soft tissues (Reijnders et al., 2017; Thomas et al., 2010). These genes likely work together to modulate the cellular environment during tissue outgrowth, contributing to the distinctive nasal elongation seen in certain cichlid species.

In the forehead region, characterized in some species by a hypertrophic nuchal hump, *ago3* (argonaute 3) has been identified (Lecaudey et al., 2019). This gene belongs to the Argonaute family involved in RNA interference and gene silencing. Through its regulatory influence on post-transcriptional gene expression, AGO3 may modulate the activity of other morphogenetic genes during forehead development, particularly those involved in ECM production or cell proliferation. In human, the function of AGO3 has been linked to in facial morphogenesis including forehead, nasal and palpebral tissues (Tokita et al., 2015). Thus, its expression in the forehead region suggests a role in finely tuning gene expression programs during soft tissue thickening or expansion, although functional studies are still needed to elucidate the exact mechanisms.

In the upper lip region, a different set of genes, including *kcnj16*, *kcnj2a*, and *cyp1a*, appear to mediate region-specific soft tissue hypertrophy (Lecaudey et al., 2021). *Kcnj16* and *kcnj2a* encode inward-rectifier potassium channels, which regulate cellular membrane potential and ionic balance, potentially influencing cell volume and tissue tension in lip outgrowth areas (Lecaudey et al., 2021). These ion transporters may indirectly affect signaling pathways or mechanical properties of cells during hypertrophy. CYP1A, a member of the cytochrome P450 family, is involved in xenobiotic metabolism and may modulate local oxidative states, contributing to localized tissue remodeling or differentiation (Linnenkamp et al., 2020; Stuppia et al., 2011). Together, these genes suggest a complex interplay between bioelectric signaling, metabolism, and tissue growth in shaping the unique upper lip profiles of certain cichlid species.

In parallel, inflammatory and immune-related genes have also been implicated in region-specific facial traits, particularly in the forehead and upper lip. In the forehead, CD163, a scavenger receptor expressed by macrophages, and SOCS2 (Suppressor of Cytokine Signaling 2), which modulates cytokine responses (Lecaudey et al., 2019), point to a role for immune regulation in soft tissue hypertrophy. These genes may contribute to the regulation of inflammation during active tissue growth or maintenance of tissue homeostasis in hypertrophic zones, especially in contexts of rapid remodeling or expansion (Farquharson and Ahmed, 2013; Greenhalgh et al., 2005; Greenhalgh and

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Alexander, 2004; MacRae et al., 2009; Metcalf et al., 2000; Sandell et al., 2015; Vos et al., 2005). The upregulation of immune genes in this region underscores the emerging view that developmental and immune pathways are deeply intertwined.

In the upper lip specific hypertrophy, GIMAP8 (GTPase of the immunity-associated protein family) has been identified (Lecaudey et al., 2021). Known for roles in lymphocyte survival and immune modulation (Zhang et al., 2024), GIMAP8 may influence lip tissue morphogenesis by shaping the local immune environment, possibly affecting cell turnover or response to mechanical stress during lip growth (Manousaki et al., 2013). The presence of inflammatory regulators in facial tissues further suggests that localized immune activity may serve as a permissive or modulatory factor during morphogenesis, rather than being restricted to host defense.

Conclusions

Facial soft tissue morphogenesis represents a complex and largely understudied frontier in developmental biology; one shaped by the interplay of genetic regulation, cellular plasticity, and evolutionary innovation. Cichlid fishes offer a uniquely powerful model for unraveling the mechanisms driving facial soft tissue diversity, thanks to their rich natural variation and experimental accessibility. Importantly, the genes involved in shaping facial soft tissues often serve multiple roles across different biological processes. For instance, regulators like *adam12*, known for roles in ECM remodeling, may also influence signaling environments and cell behavior, demonstrating how a single gene can contribute to distinct outcomes depending on context. This genetic pleiotropy begs the need to move beyond linear gene-function models and toward integrative frameworks that consider how genetic networks interact within dynamic multidimendional developmental landscapes. Cichlid models now position us to explore these complexities at both molecular and evolutionary scales. As we begin to map the genetic architecture underlying soft tissue variation, we not only deepen our understanding of vertebrate facial development but also lay the groundwork for translational insights into human facial diversity and congenital disorders.

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