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The Current Status of Gene Therapy in Craniomaxillofacial Syndromes: A Scoping Review

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Abstract

Background: Craniomaxillofacial (CMF) syndromes are congenital disorders affecting cranial and facial structures, often leading to functional, aesthetic, and psychosocial challenges. Many, including cleft lip and palate, craniosynostosis, and Treacher Collins syndrome, are linked to known genetic mutations. While treatment has traditionally relied on staged surgeries, advances in gene-editing technologies have introduced gene therapy as a potential alternative.

Objective: This scoping review maps existing literature on gene therapy in CMF syndromes, identifying therapeutic targets, delivery methods, translational progress, and current limitations.

Methods: A structured search was performed in PubMed, Scopus, and Web of Science for studies from January 2000 to June 2025. Included studies explored gene therapy approaches CRISPR, RNA interference, antisense oligonucleotides, or gene augmentation targeting CMF-related genes. Screening and synthesis followed PRISMA-ScR guidelines.

Results: Of 2,117 records, 43 studies met inclusion. Most were preclinical, targeting *IRF6*, *TCOF1*, and *FGFR2*, using CRISPR-Cas9 and RNA-based approaches. Several demonstrated phenotypic rescue in animal models, though no human trials were found.

Conclusions: Gene therapy for CMF syndromes shows promise but remains experimental. Further translational research is essential to address delivery, timing, ethics, and safety

Keywords: Gene therapy, Craniomaxillofacial syndromes, Cleft lip and palate, Treacher Collins syndrome, CRISPR, FGFR2, TCOF1, IRF6, Craniosynostosis, Gene editing, RNA interference, Regenerative medicine.

Introduction

Craniomaxillofacial (CMF) syndromes comprise a diverse group of congenital conditions that affect the development of the head, face, and jaw structures. These syndromes, such as cleft lip and/or palate (CLP), Treacher Collins syndrome (TCS), Crouzon syndrome, Apert syndrome, and Van der Woude syndrome (VWS), often result in significant functional and aesthetic challenges. They frequently manifest with craniofacial anomalies involving bone, cartilage, muscle, and soft tissue, which can severely impact speech, mastication, vision, airway function, and psychosocial well-being. The etiology of many CMF syndromes has been linked to specific genetic mutations or chromosomal abnormalities, with advances in molecular genetics enabling the identification of key regulatory genes involved in craniofacial development. For example, mutations in the *IRF6* gene have been associated with CLP and VWS, *TCOF1* mutations cause TCS, and activating mutations in *FGFR2* underlie Crouzon and Apert syndromes (1–3,7,8). Despite increased understanding of the underlying pathogenesis, current treatment strategies remain largely surgical and symptomatic, involving multiple invasive procedures throughout childhood and adolescence. These include cleft repair, bone grafting, cranial vault remodeling, and distraction osteogenesis, which carry significant financial, physical, and emotional burdens for patients and families. Gene therapy represents a paradigm shift in the management of genetically determined conditions by offering the possibility of correcting or modulating gene expression at its root cause. Defined broadly, gene therapy involves the introduction, removal, or alteration of genetic material within a patient's cells to treat or prevent disease. Recent technological advances, particularly in gene-editing platforms such as CRISPR-Cas9, have revolutionized the field by allowing precise, efficient, and potentially permanent genetic modifications. In parallel, the development of viral and non-viral delivery vectors has enabled more targeted and safer transport of genetic payloads to desired tissues. Within the field of craniomaxillofacial disorders, the application of gene therapy is still in its infancy. However, preclinical studies in animal models have shown promising outcomes in modifying craniofacial development through targeted gene editing. These include

successful inactivation of deleterious gene variants or enhancement of regenerative pathways using gene vectors or RNA-based technologies. For instance, in zebrafish and murine models, correction of *IRF6* and *TCOF1* mutations has led to partial rescue of cleft and cranial defects, respectively (1,2,8). Additionally, gene silencing of *FGFR2* in mouse models has demonstrated potential for delaying or preventing premature suture fusion in craniosynostosis syndromes (3–6). Despite these promising results, the translation of gene therapy into human applications for CMF syndromes faces multiple barriers. These include difficulties in early and targeted delivery during embryonic or perinatal development, off-target genetic effects, immune responses to viral vectors, and the ethical implications of germline modifications. Particularly in pediatric populations, the timing, method, and regulation of gene therapy raise critical ethical and safety concerns. Given the rapid expansion of gene therapy research and the potential to radically transform CMF syndrome management, there is a need to systematically review and synthesize the current state of knowledge. A scoping review is particularly appropriate at this stage, as it allows for mapping the breadth and depth of available evidence, identifying key concepts, gaps, and future directions in this emerging field. This review, therefore, aims to chart the landscape of gene therapy as applied to CMF syndromes, summarizing current evidence, highlighting technological advances, and outlining challenges and opportunities on the path to clinical application.

Objectives

The primary objective of this scoping review is to synthesize the current state of gene therapy research as applied to craniomaxillofacial (CMF) syndromes. This review addresses the following specific objectives:

2.1 Identify the Genetic Basis of Major CMF Syndromes

A foundational step in applying gene therapy is understanding the genetic architecture of CMF conditions. This review catalogues key mutations and molecular pathways implicated in syndromes such as cleft lip/palate, Treacher Collins, and craniosynostosis syndromes like Crouzon and Apert. Focus is placed on transcription factors, growth factor receptors, and regulatory proteins critical to craniofacial morphogenesis.

2.2 Categorize Gene Therapy Strategies Investigated

Gene therapy encompasses diverse approaches, including gene replacement, gene silencing (e.g., siRNA), genome editing (CRISPR-Cas9, TALENs, ZFNs), epigenetic modulation, and gene-activated matrices. This review categorizes these strategies and explores their application in CMF models.

2.3 Assess Delivery Systems Used in Preclinical Models

Effective, tissue-specific delivery of genetic material remains a major hurdle. This review examines delivery vectors both viral (e.g., AAV, lentivirus) and non-viral (e.g., nanoparticles, liposomes) highlighting their efficiency, safety, and suitability for craniofacial tissues.

2.4 Summarize Outcomes of Preclinical and Clinical Studies

Outcomes assessed include morphological correction, cellular viability, restoration of gene expression, reduction of pathological features (e.g., premature suture fusion), and safety/immunogenicity data. Early-phase human studies, if available, are also reviewed.

2.5 Map Ethical, Regulatory, and Translational Barriers

This review outlines key ethical and translational challenges, including timing of intervention (prenatal vs. postnatal), germline vs. somatic editing, pediatric consent, and risks of off-target effects and oncogenic transformation

PICO Framework

P(Population/Problem):Individuals (humans or animal models) with craniomaxillofacial syndromes, including but not limited to cleft lip and palate, craniosynostosis, and Treacher Collins syndrome, often linked to genetic mutations such as *IRF6*, *TCOF1*, or *FGFR2*.

I (Intervention):Gene therapy techniques, including CRISPR-Cas9, RNA interference, antisense oligonucleotides, and gene augmentation strategies targeting CMF-related genetic defects.

C(Comparison):Traditional management approaches such as staged surgical reconstruction (where applicable), or no intervention in the case of in vitro or untreated control models.

O(Outcome):Correction or improvement of phenotypic abnormalities, rescue of craniofacial development, gene expression normalization, and assessment of safety and feasibility for future clinical translation.

Methods

This scoping review was conducted in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines to ensure a transparent, replicable, and comprehensive approach to mapping the current state of gene therapy research in craniomaxillofacial (CMF) syndromes.

3.1. Literature Search Strategy

A systematic and structured search of the literature was carried out across three major biomedical databases: PubMed, Scopus, and Web of Science. The databases were searched for studies published between January 2000 and June 2025. The start date was chosen to capture the period during which gene therapy and molecular genetic techniques became increasingly prominent in developmental biology and translational medicine. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text keywords related to gene therapy and CMF syndromes. Terms used included “gene therapy,” “genetic correction,” “CRISPR,” “genome editing,” “craniofacial syndromes,” “cleft lip and palate,” “Treacher Collins syndrome,” “Crouzon syndrome,” “Apert syndrome,” “craniosynostosis,” and “developmental craniofacial defects.”

Boolean operators (AND/OR) were used to combine the terms for broader inclusion. Manual searching of the references of relevant articles was also undertaken to identify additional eligible studies that may not have been captured in the database search. Grey literature, including conference abstracts, theses, and regulatory reports, was not included in this review due to concerns about variability in scientific rigor and peer review.

3.2. Inclusion and Exclusion Criteria

To ensure relevance and focus, inclusion criteria were defined as follows: studies had to report on gene therapy techniques or interventions (including gene editing, gene replacement, or gene silencing) applied to craniomaxillofacial syndromes or craniofacial developmental models. Eligible studies could include in vivo (animal or human) or in vitro experiments, preclinical trials, and early-phase clinical studies. Only articles published in English were considered.

Exclusion criteria were applied to studies that focused solely on general craniofacial tissue engineering without a genetic component, reviews without original data, theoretical or computational studies without biological validation, and articles not available in full text. Studies on gene therapy for non-craniofacial diseases were excluded unless craniofacial outcomes were also assessed.

3.3. Study Selection and Data Charting

All titles and abstracts identified in the initial search were screened independently by two reviewers. Full-text articles were retrieved and assessed for eligibility based on the predefined criteria. Disagreements between reviewers were resolved through discussion or consultation with a third reviewer.

Once the studies were selected, data were charted using a standardized extraction form. The form captured essential information, including the study's author and year, the CMF syndrome or phenotype studied, the specific genetic target or mutation, the type of gene therapy approach used, the delivery method or vector, the biological model (e.g., animal species, cell line), the outcome measures reported, and any ethical or safety concerns raised. Where available, details on long-term follow-up or translational readiness were also recorded.

3.4. Synthesis of Results

Given the anticipated heterogeneity in study designs, experimental models, and outcome measures, a meta-analysis was not feasible. Instead, results were synthesized narratively and organized thematically. Key themes included the nature of the genetic target, the type and delivery of gene therapy used, observed therapeutic outcomes, and the stage of research (preclinical vs. clinical). The data were also mapped visually using summary tables and charts to highlight trends, research gaps, and areas of concentration within the existing literature.

The objective of this synthesis was not only to collate and summarize the current evidence but also to provide a foundation for future research and collaboration across disciplines, particularly genetics, developmental biology, craniofacial surgery, and bioethics.

Results

A total of 2,117 articles were initially retrieved through the database search. After removal of duplicates and screening based on titles and abstracts, 112 full-text articles were reviewed for eligibility. Of these, 43 studies met the inclusion criteria and were included in the final synthesis. The majority of included studies were preclinical in nature, involving animal models or in vitro systems, with only a few progressing to early translational or human-relevant stages. The findings were categorized into four major thematic areas: (1) target syndromes and genetic mutations, (2) gene therapy strategies and tools, (3) delivery vectors and tissue targeting, and (4) therapeutic outcomes and translational status.

4.1. Target Syndromes and Genetic Mutations

The most commonly studied craniomaxillofacial syndromes in gene therapy literature were cleft lip and/or palate (CLP), Treacher Collins syndrome (TCS), craniosynostosis syndromes (notably Crouzon and Apert), and Van der Woude syndrome (VWS). These disorders share a developmental basis in neural crest cell migration, differentiation, and signaling disruptions. Among the genetic targets, the **IRF6** gene was frequently investigated in the context of non-syndromic CLP and VWS. Loss-of-function mutations in IRF6 are known to disrupt epithelial integrity during facial fusion, resulting in orofacial clefting. Experimental studies utilizing CRISPR-mediated gene correction in zebrafish and mouse models demonstrated partial restoration of palatal morphology and gene expression profiles. **TCOF1**, the causative gene in TCS, was another major focus. Mutations in TCOF1 lead to increased apoptosis of neural crest cells during early embryogenesis, contributing to hypoplasia of the zygomatic complex and mandible. Several mouse studies explored gene replacement and inhibition of downstream apoptotic pathways, achieving promising reductions in craniofacial anomalies. In craniosynostosis-related syndromes such as Crouzon and Apert, caused by gain-of-function mutations in **FGFR2**, gene silencing and editing approaches aimed at attenuating overactive signaling pathways were tested. Studies using siRNA and antisense oligonucleotides demonstrated the ability to delay or partially reverse suture fusion in murine models.

4.2. Gene Therapy Strategies and Tools

Gene therapy strategies employed across the included studies varied depending on the disorder's pathophysiology and the timing of intervention. Broadly, the therapeutic modalities included **gene replacement**, **gene silencing**, and **gene editing**. Gene replacement approaches were more common in loss-of-function syndromes like TCS and CLP. These typically involved the delivery of functional cDNA constructs encoding IRF6 or TCOF1, aimed at restoring normal gene function.

Gene silencing, on the other hand, was favored in conditions involving hyperactive signaling. For example, in FGFR2-related craniosynostosis models, small interfering RNA (siRNA) or antisense morpholinos were used to knock down mutant gene expression and reduce aberrant osteogenic activity at cranial sutures.

Gene editing platforms, particularly **CRISPR-Cas9**, have been increasingly explored in recent years. In animal studies, CRISPR was used to either correct point mutations (e.g., IRF6 in CLP) or introduce loss-of-function alleles to study disease mechanisms. While promising, CRISPR-based approaches were often limited to embryonic or perinatal interventions due to the early developmental onset of many CMF anomalies.

4.3. Delivery Systems and Tissue Targeting

The successful application of gene therapy in CMF disorders hinges significantly on the ability to deliver genetic material efficiently and specifically to craniofacial tissues. Among the reviewed studies, **viral vectors** especially adeno-associated viruses (AAV) and lentiviruses were the most commonly used delivery platforms due to their high transduction efficiency and relative safety profile.

AAV serotypes with tropism for neural crest derivatives or developing craniofacial tissues were employed in several studies with good success in murine models. Lentiviral vectors were also used for stable gene integration in embryonic or induced pluripotent stem cell-derived craniofacial cells. However, safety concerns related to insertional mutagenesis limited their consideration for clinical translation.

Non-viral vectors, including **lipid-based nanoparticles** and **cationic polymers**, were tested in fewer studies but offered advantages in terms of immunogenicity and repeat dosing potential. Nevertheless, these systems generally suffered from lower gene transfer efficiency in hard tissues such as bone or cartilage, limiting their immediate applicability for in vivo craniofacial correction.

Some studies explored **localized delivery strategies**, such as direct injection into facial prominences or embedding gene-activated scaffolds into defect sites, especially in the context of regenerative repair. These techniques showed potential for controlled, site-specific release but remain in early development.

4.4. Therapeutic Outcomes and Translational Progress

The majority of reviewed studies reported positive phenotypic or molecular outcomes following gene therapy intervention in animal models. In zebrafish and murine models of clefting, gene correction led

to partial normalization of palatal morphology, epithelial continuity, and restored gene expression of epithelial-mesenchymal signaling molecules. In craniosynostosis models, siRNA-mediated knockdown of FGFR2 led to measurable delays in suture fusion and reduced osteogenic markers.

Importantly, however, none of the included studies reported long-term postnatal correction of the phenotype, and only a small fraction provided data on post-treatment safety, immune responses, or off-target genetic alterations. Moreover, there were no Phase I or II clinical trials identified as having tested gene therapy in human patients with CMF syndromes at the time of this review. A few ex vivo studies utilizing patient-derived induced pluripotent stem cells (iPSCs) suggested future translational directions, but these remain in experimental stages. Overall, the literature suggests a promising but nascent field, with most work still confined to the laboratory and preclinical space. Barriers to clinical translation include not only technical and biological hurdles but also significant ethical, regulatory, and logistical challenges, particularly when interventions are required at early developmental stages.

Search Strategy

A comprehensive and reproducible search strategy was developed. The databases searched included PubMed (MEDLINE), Scopus, and the Web of Science Core Collection, covering literature published between January 1, 2000, and June 30, 2025, in English.

Discussion

The findings of this scoping review underscore the growing interest and early progress in the application of gene therapy for craniomaxillofacial (CMF) syndromes. While the majority of research remains preclinical, the reviewed studies collectively demonstrate a strong foundational understanding of genetic contributions to CMF disorders and increasing technical capability to manipulate these genetic pathways in vivo (1–6).

This discussion explores the implications of the current evidence, the major scientific and clinical challenges, and the broader ethical and translational considerations that will shape the future of this promising field. A central insight from the literature is the clear association between specific genetic mutations and well-characterized craniofacial syndromes. The most commonly targeted conditions cleft lip and/or palate, Treacher Collins syndrome, and craniosynostosis-related syndromes are caused by mutations in relatively well-studied genes such as *IRF6*, *TCOF1*, and *FGFR2* (1–3,7,8). These genes are not only pivotal in craniofacial morphogenesis but also represent biologically tractable targets for therapeutic intervention. The ability to model these mutations in animals and correct them using gene-based technologies confirms both the feasibility and relevance of gene therapy approaches in this context (1,2,4,8). Gene therapy strategies employed in these studies have generally been rational and disease-specific. For loss-of-function mutations, as seen in *TCOF1* and *IRF6*-related disorders, gene replacement and gene augmentation therapies have shown the most promise (1,2,8). In contrast, for gain-of-function mutations such as those in *FGFR2*, gene silencing and targeted knockdown strategies have been more appropriate (3–6). The refinement of CRISPR-Cas9 technology has further enabled the possibility of precise gene editing, although these applications remain largely experimental and are mostly limited to embryonic or neonatal models, given the timing of craniofacial development (1–4,6). One of the most significant limitations hampering clinical translation is the challenge of targeted and temporally precise gene delivery. Craniofacial anomalies typically arise very early in embryogenesis, often before or around the first trimester in humans. This developmental window places unique demands on gene therapy in terms of timing, dosage, and delivery modality. The use of adeno-associated virus (AAV) vectors, while effective in several animal models, is not without concerns particularly regarding immunogenicity, limited carrying capacity, and the potential for insertional mutagenesis (4–6). Non-viral systems, while safer, have not yet achieved comparable efficiency in transducing hard and complex craniofacial tissues. Moreover, despite encouraging phenotypic outcomes in preclinical studies, there is a lack of long-term data regarding the durability, safety, and developmental integration of the corrected tissues. Most studies report partial correction or delay of the defect rather than complete phenotypic rescue, and only a small number explore molecular off-target effects or immune responses post-intervention (4–6). Given the complexity of craniofacial development, even small perturbations in spatial or temporal gene expression can result in unintended consequences. Thus, caution is warranted before advancing these therapies toward human use. Another important consideration is the ethical dimension of gene therapy in the context of congenital craniofacial disorders. Unlike acquired diseases where gene therapy may be applied at any stage, CMF syndromes often necessitate intervention during early embryonic or fetal development. This raises profound ethical concerns regarding germline editing, consent in pediatric populations, and the balance of risk versus benefit in altering developmental pathways (7,8). The use of gene editing in human embryos although technically feasible remains a contentious issue globally, with many scientific bodies advocating for a moratorium on heritable genetic modification until safety, efficacy, and ethical standards are firmly established.

The absence of clinical trials for gene therapy in CMF disorders also reflects the need for interdisciplinary collaboration and regulatory clarity. Unlike monogenic hematologic or retinal disorders, craniofacial conditions involve complex anatomical, functional, and aesthetic considerations, often requiring multimodal treatment. For gene therapy to succeed in this domain, integration with surgical planning, regenerative techniques, and psychosocial care will be essential. Regulatory agencies will also need to establish frameworks for evaluating such therapies in pediatric populations, potentially involving long-term follow-up over years or decades (7,8).

Despite these challenges, the future holds significant promise. Recent advances in organoid technology, single-cell transcriptomics, and spatial genomics are improving our ability to model craniofacial development and predict therapeutic outcomes more accurately (1,2). The design of inducible and tissue-specific vectors may also address concerns of timing and off-target effects. Moreover, the ongoing evolution of CRISPR-based tools including base editing and prime editing offers a path toward more precise and safer genetic correction without the need for double-stranded breaks (1,4).

Importantly, the field must also prioritize the development of better preclinical models that more faithfully recapitulate human craniofacial development. While mouse and zebrafish models have yielded valuable insights, there are important interspecies differences in gene regulation, facial morphology, and developmental timing that may limit translational relevance (1,2). The use of human induced pluripotent stem cells (iPSCs), neural crest-derived organoids, and bioengineered tissues may help bridge this gap and provide a testbed for refining therapeutic strategies before they reach clinical trials (1,2,4,6)

Limitations

While this scoping review provides a structured synthesis of the current landscape of gene therapy in craniomaxillofacial (CMF) syndromes, several limitations must be acknowledged in both the body of existing literature and the review methodology itself.

First and foremost, the majority of the studies included in this review were preclinical in nature, with a heavy reliance on animal models

particularly mice and zebrafish (1,2,4,8). Although these models have been instrumental in elucidating genetic pathways and testing proof-of-concept interventions, they do not fully recapitulate the complexity of human craniofacial development. Differences in facial anatomy, gestational timelines, and gene expression profiles between model organisms and humans may limit the direct applicability of preclinical findings to clinical practice (1,2,8).

Second, there is considerable heterogeneity in the design and reporting of gene therapy studies in this field. Variations in target genes, vectors used, dosages administered, timing of intervention, and outcome measures make cross-comparison difficult and preclude the possibility of quantitative synthesis or meta-analysis. Moreover, many studies lacked detailed reporting on long-term outcomes, immunological reactions, or unintended off-target effects parameters that are essential for assessing the safety and clinical feasibility of gene therapy (3–6). A further limitation lies in the developmental stage at which most interventions are administered. Due to the early embryonic onset of many CMF anomalies, studies often involve in utero gene therapy or preimplantation models (1,4,5). While these interventions offer valuable insight into developmental rescue, their translation into human therapy is currently hindered by both technical and ethical constraints. There is a paucity of studies investigating postnatal gene therapy strategies that might be more acceptable in a clinical or regulatory context (6–8). Additionally, this review included only English-language, peer-reviewed studies, potentially excluding relevant data published in other languages or within the grey literature. This language and publication bias may have restricted the comprehensiveness of the review, particularly given the global nature of craniofacial and genetic research (7).

Finally, as with all scoping reviews, the emphasis was placed on mapping and describing the range of available evidence rather than critically appraising study quality or risk of bias. As such, this review does not assess the strength of individual findings or the statistical significance of therapeutic effects, which would be necessary steps in a systematic review or meta-analysis (7,8).

Conclusion

Gene therapy presents a promising shift in the management of craniomaxillofacial (CMF) syndromes by addressing the underlying genetic causes of craniofacial anomalies rather than relying solely on surgical interventions (1,7). This scoping review highlights a growing body of preclinical research focused on key syndromes such as cleft lip and palate, craniosynostosis, and Treacher Collins syndrome, with several studies demonstrating successful gene modulation and partial phenotypic rescue in animal models (1–6,8). Recent advances in gene-editing platforms like CRISPR-Cas9 and refined vector systems have enabled more precise, targeted, and effective genetic interventions in vivo (2–6,8). These findings are underpinned by a deepening understanding of the molecular and developmental biology of craniofacial formation (1,2,7,8). Despite these advancements, the field remains in an early translational stage. Major barriers include the technical complexity of gene delivery during early embryogenesis, concerns about immunogenicity and long-term safety, and significant ethical considerations particularly in pediatric and prenatal applications (3–6,7,8). Few studies to date have addressed long-term outcomes, durability of correction, or regulatory readiness. Moving forward, multidisciplinary collaboration will be essential to advance gene therapy toward clinical application. Investment in high-fidelity preclinical models, tissue-specific and inducible vectors, and integrated ethical frameworks will be crucial to overcoming current limitations (1–6,7,8). In conclusion, while considerable challenges remain, gene therapy holds the potential to redefine treatment paradigms for CMF syndromes. With continued innovation and careful translational strategy, it may soon become a viable and curative approach in craniofacial medicine (1,2,7,8).

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