CEP Clinical and Experimental Pediatrics [Epub ahead of print]
https://doi.org/10.3345/cep.2026.02299

Review article

# Suture stem cells in pediatric craniosynostosis: pathophysiological mechanisms, surgical management, and emerging regenerative therapies

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Craniosynostosis (CS) is a complex congenital disorder characterized by the premature fusion of one or more cranial sutures resulting from interactions between genetic alterations, environmental influences, and the dysregulated differentiation of cranial suture stem cells (SuSCs). Increasing evidence indicates that SuSC homeostasis disruption, including alterations in glioma-associated oncogene homolog 1-positive, axis inhibition protein 2-positive, and other stem/progenitor cell populations, along with aberrant regulation of developmental signaling pathways, plays a central role in the pathogenesis of CS. This review summarizes current advances in SuSC biology and the molecular mechanisms of, diagnostic approaches for, and therapeutic strategies for CS. By integrating evidence from studies published in 2000–2026, we discuss how genetic mutations and signaling pathways, including the fibroblast growth factor, bone morphogenetic protein, Wnt, and Hedgehog pathways, influence SuSC maintenance, lineage commitment, and osteogenic differentiation. We further summarize recent clinical advances, including virtual surgical planning, three-dimensional printing, and endoscope-assisted minimally invasive techniques, as well as emerging molecular and stem cell-based regenerative strategies aimed at restoring functional cranial suture structures. By connecting genetic mechanisms, stem cell biology, and translational medicine, this review provides an integrated framework to increase our understanding of the pathogenesis of CS and highlights potential directions for the development of mechanism-based therapies to improve long-term craniofacial and neurodevelopmental outcomes.

**Key words:** Craniosynostosis, Suture mesenchymal stem cells, Stem cell niche, Stem cell therapy, Molecular therapy

## Key message

Craniosynostosis involves the disruption of cranial suture stem cell homeostasis and niche regulation as well as premature osteogenesis. Its current treatment remains primarily surgical, while emerging molecular, biomaterial, and stem cell-based strategies may complement structural correction. Understanding the interactions between cranial suture stem cells, developmental signaling, and biomechanical influences may support more biologically informed treatments.

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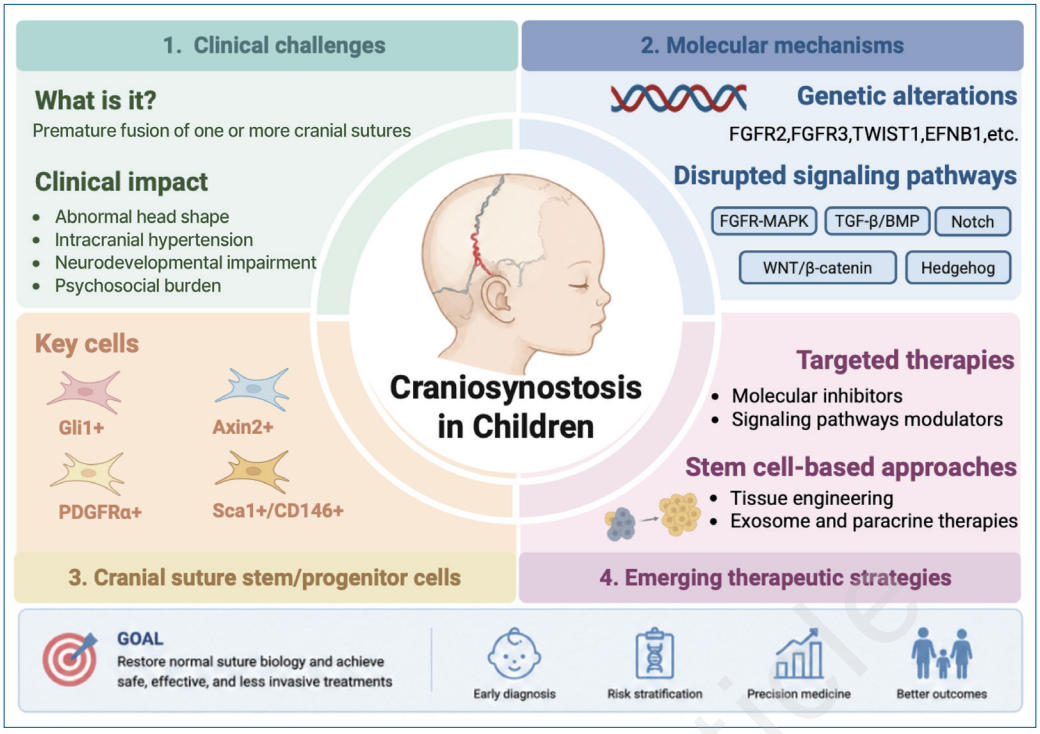
## Introduction

Craniosynostosis (CS), a congenital disorder characterized by the premature closure of cranial sutures, has an estimated prevalence of approximately 1/2100–1/2500.[1] According to its predominant pathogenesis, CS is categorized into nonsyndromic and syndromic types.[2] Nonsyndromic CS is characterized by a cephalic deformity. Sagittal synostosis is the most common subtype, accounting for approximately 50% of nonsyndromic cases, followed by unilateral coronal synostosis, accounting for approximately 15% of cases.[3] Syndromic CS is associated with broader craniofacial abnormalities including Apert syndrome, Pfeiffer syndrome, Crouzon syndrome, Jackson-Weiss syndrome, and Boston-type CS syndrome.[4] Patients with CS, particularly syndromic CS, may develop complications such as intracranial hypertension and visual disturbances.[5,6] Without timely intervention for CS, premature suture fusion may restrict cranial growth, increase intracranial pressure, and contribute to neurodevelopmental impairment or permanent neurological deficits.[2]

The cranial suture is not merely a fibrous connection

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Received: 28 July 2026, Revised: 7 September 2026, Accepted: 9 September 2026

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**Graphic abstract.** FGFR2, fibroblast growth factor receptor 2; FGFR3, fibroblast growth factor receptor 3; TWIST1, twist family bHLH transcription factor 1; EFNB1, ephrin-B1; FGFR, fibroblast growth factor receptor; MAPK, mitogen-activated protein kinase; TGF-β, transforming growth factor-β; BMP, bone morphogenetic protein; WNT, wingless-related integration site; Gli1, glioma-associated oncogene homolog 1; Axin2, axis inhibition protein 2; PDGFRα, platelet-derived growth factor receptor α; Sca1, stem cell antigen-1; CD146, cluster of differentiation 146.

between adjacent calvarial bones; rather, it is a major site of postnatal cranial expansion and specialized stem cell niche. During skull growth, osteoid is deposited at the osteogenic fronts, bony surfaces undergo continuous remodeling, and brain expansion generates centrifugal forces that contribute to calvarial enlargement.[3] The suture mesenchyme contains stem and progenitor cells, osteoblast lineage cells, osteoclasts, and extracellular matrix components. Among them, suture stem cells (SuSCs) play a central role in maintaining suture patency, supporting calvarial growth, and promoting post-injury repair.[7,8]

SuSCs primarily originate from 2 distinct embryonic lineages: the paraxial mesoderm and the cranial neural crest. Their developmental origin varies according to the anatomical location of the sutures. For example, SuSCs in the sagittal sutures are predominantly derived from the cranial neural crest, whereas those in the coronal sutures originate from the paraxial mesoderm. These lineage-specific differences may contribute to variations in cellular behavior, differentiation potential, and pathological fusion susceptibility.[9] The importance of SuSCs in CS has been noted, and studies have revealed that reduced cell numbers, population imbalances, and dysregulated fate commitment may contribute to premature cranial suture fusion.[10]

Maintenance of cranial suture patency depends on the coordinated regulation of SuSC self-renewal, proliferation, lineage commitment, and osteogenic differentiation. Disruption of this cellular equilibrium is increasingly recognized as the central mechanism underlying CS. Genetic variants and environmental or biomechanical factors can act as upstream modifiers of SuSC behavior.[11] To date, variants in more than 70 different genes have been associated with CS pathogenesis, including fibroblast growth factor receptors (FGFRs), Twist family bHLH transcription factor 1 (TWIST1), ephrin B1 (EFNB1), transcription factor 12 (TCF12), and mothers against decapentaplegic homolog family member 6 (SMAD6).[12] Mechanical forces, endocrine factors, and toxic exposure during embryonic development may also modify the disease risk, although their interactions with SuSC biology remain unclear (Fig. 1).

Given the central role of SuSCs in cranial suture homeostasis and pathological fusion, here we summarize the major marker-defined SuSC populations, signaling pathways that regulate their fate decisions, and mechanisms through which their dysregulation contributes to premature suture fusion. We also discuss the contemporary surgical management and emerging molecular and stem

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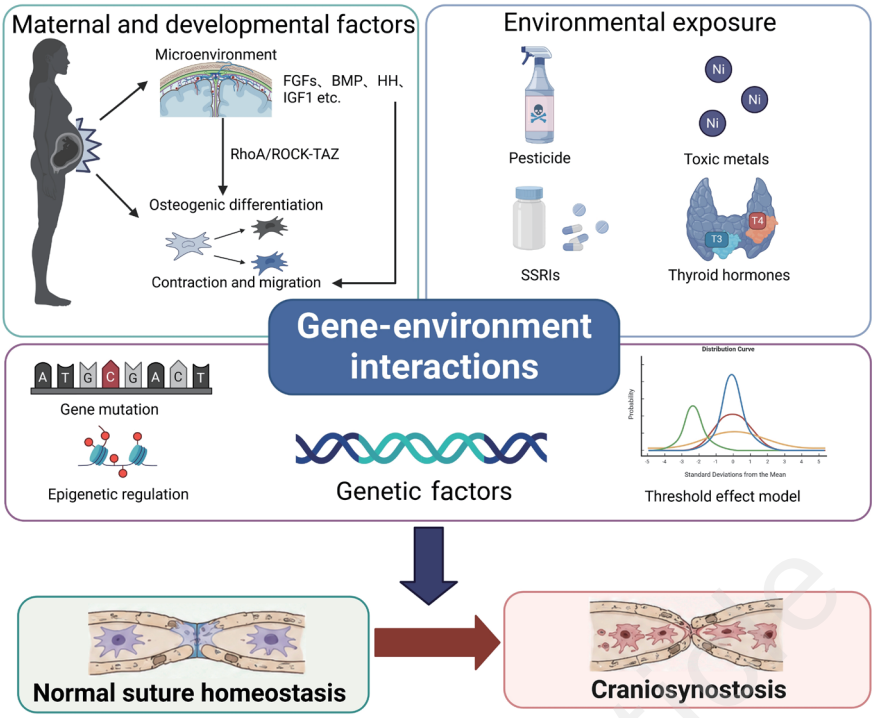



**Fig. 1.** Gene and environment in the pathogenesis of craniosynostosis. The pathogenesis of craniosynostosis involves complex interactions between genetic and environmental factors. Genetic predisposition and environmental exposures converge to influence the behavior and fate of suture stem cells, ultimately disrupting their normal osteogenic differentiation and leading to premature suture fusion. These contributory factors can be broadly categorized into genetic determinants, maternal factors, and external environmental exposures. FGFs, fibroblast growth factors; BMP, bone morphogenetic protein; HH, hedgehog; IGF1, insulin-like growth factor 1; RhoA/ROCK–TAZ, Ras homolog family member A/Rho-associated protein kinase–transcription coactivator with PDZ-binding motif; SSRIs, selective serotonin reuptake inhibitors.

cell=based therapeutic strategies, with an emphasis on exploring the potential for functional suture reconstruction.

## Literature search and study selection

A structured search was conducted of PubMed/MEDLINE and the Web of Science Core Collection for studies published between January 1, 2000, and August 31, 2026. The literature search and study selection process was structured with reference to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and PRISMA-S frameworks to enhance transparency and reproducibility. As the review encompassed basic, translational, and clinical evidence rather than a single intervention-based question, the search was organized into 5 predefined domains: (1) core CS; (2) genetics and molecular pathogenesis; (3) SuSCs (with synonyms such as mesenchymal stem cells [MSCs] and suture mesenchymal stem cells [SMSCs]); (4) clinical management, surgery, and regenerative medicine; and (5) environmental and maternal factors. The titles and abstracts were screened for relevance, followed by a full-text assessment according to the predefined eligibility criteria. The reference lists of the key included studies and relevant evidence syntheses were also examined, and a forward citation search was performed to identify eligible studies that were not captured in the electronic search. The study selection process is summarized in the PRISMA flow diagram (Fig. 2). The complete database-specific search terms and search strategies, as well as the predefined inclusion and exclusion criteria used for the study selection, are provided in the Supplementary Materials.

## Stem cells in CS

### 1. Cranial suture niche in calvarial expansion, homeostasis, and pathological fusion

The cranial suture is a major site for intramembranous bone growth and postnatal calvarial expansion. Adjacent cranial bones are connected by a fibrous suture mesenchyme containing mesenchymal stem and progenitor cells, osteoblast lineage cells, osteoclasts, and extracellular matrix components.[13] During cranial develop-

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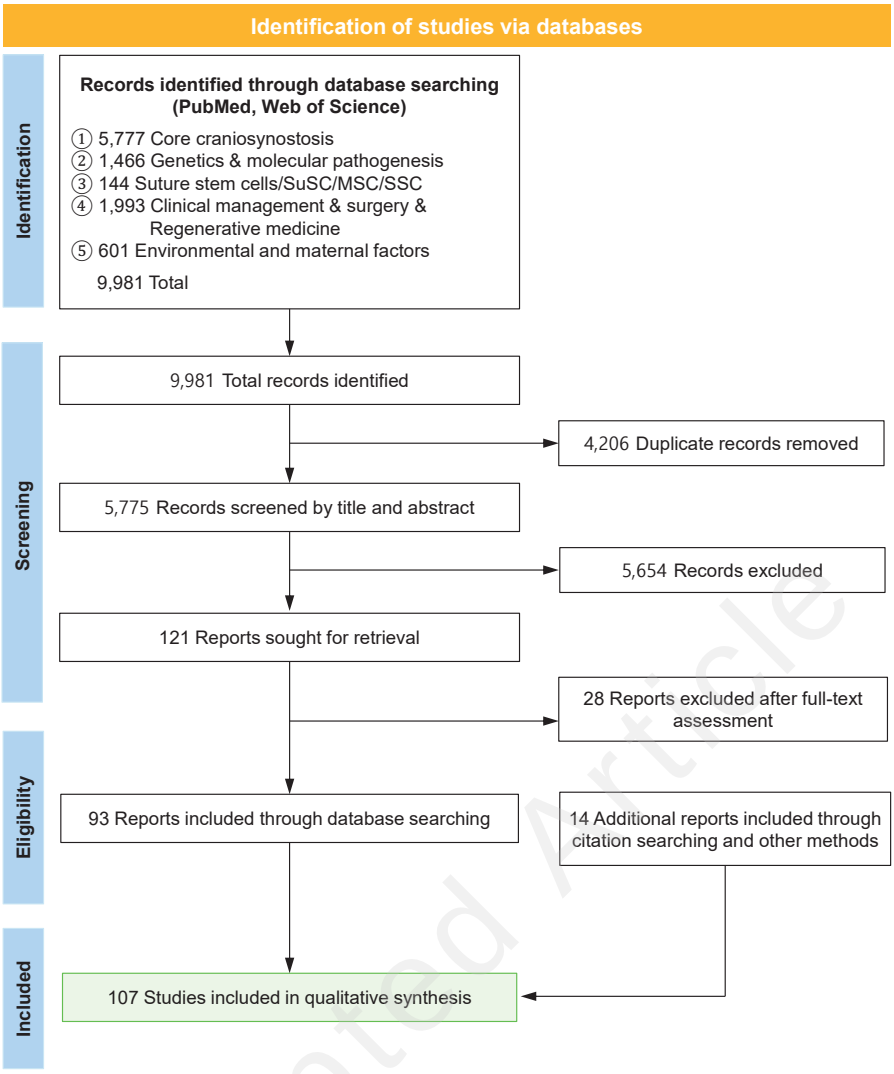



**Fig. 2.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) 2020 flow diagram of the literature search and study-selection process: Studies were identified through database searches and supplementary citation searches, followed by duplicate removal, screening, and eligibility assessment. A total of 107 studies were included in the review. SuSC, suture stem cell; MSC, mesenchymal stem cell; SSC, skeletal stem cell.

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ment, SuSCs maintain normal growth via proliferation and osteogenic differentiation. Maintaining suture patency requires a balance between the preservation of undifferentiated SuSCs within the central suture mesenchyme and controlled bone formation at adjacent osteogenic fronts.[13,14]

Premature suture fusion may occur when this balance is disrupted by genetic alterations or environmental or biomechanical disturbances. Although excessive osteogenic differentiation and a reduction in the number of SuSCs are important contributors to CS, these mechanisms do not fully explain CS. Recent evidence has indicated that premature fusion may also involve impaired self-renewal, premature lineage commitment, SuSC depletion or imbalance, and local niche dysregulation. In prematurely fused human sutures, mesenchymal cells exhibit increased expression of osteogenesis-related genes and reduced expression of stemness-related genes. [15] Experimental studies demonstrated that the altered representation of skeletal stem/progenitor cells and premature SuSC differentiation can contribute to pathological suture fusion.[10,16]

The cranial suture niche is dynamically activated during injury repair. Li et al.[17] recently demonstrated that injury-induced C-X-C motif chemokine ligand 12 (CXCL12)-CXC chemokine receptor type 4 (CXCR4) signaling promotes the proliferation and directional migration of SuSCs toward calvarial defects and induces sonic hedgehog (SHH) and Indian hedgehog (IHH) production, which further supports SuSC expansion and osteoblastic differentiation. These findings indicate that calvarial regeneration depends on coordinated niche

signaling rather than the indiscriminate stimulation of osteogenesis.

Therefore, SuSCs constitute a heterogeneous group of stem and progenitor cells with distinct roles in suture maintenance, pathological fusion, and tissue repair.

## 2. Roles of marker-defined SuSC populations in CS

SuSCs constitute a heterogeneous group of stem and progenitor cells rather than a single uniform cell population. Multiple marker-defined populations have been identified within the cranial suture niche, including glioma-associated oncogene homolog 1-positive (Gli1+), axis inhibition protein 2-positive (Axin2+), postnatal paired related homeobox 1-positive (Prrx1+), cluster of differentiation 51-positive and cluster of differentiation 200-positive (CD51+CD200+), and bone morphogenetic protein receptor type 1A-positive (BMPR1A+) cells. However, these markers should not be interpreted as being mutually exclusive. For example, Gli1, Axin2, and Prrx1 are primarily lineage-associated or signaling-responsive markers, whereas CD51 and CD200 define a prospectively isolatable surface immunophenotype of suture-resident skeletal stem/progenitor cells.[14,18-21]

Gli1+ cells represent a broadly distributed suture-resident mesenchymal stem/progenitor cell population. During postnatal development, these cells become enriched in the cranial suture mesenchyme and contribute to calvarial homeostasis and injury repair. Studies have shown that Gli1+ cells can generate cells at the osteogenic fronts, periosteal cells, dural cells, and osteocytes in the adjacent calvarial bone. Their functional importance is also supported by regenerative studies in Twist1+/- mice, in which the transplantation of Gli1+ MSCs combined with a biodegradable scaffold regenerated a functional cranial suture, improved skull morphology, normalized intracranial pressure, and ameliorated neurocognitive abnormalities.[14,22]

Axin2+ cells were predominantly enriched within the suture midline and represented a more spatially restricted SuSC population. These cells exhibit long-term self-renewal, clonal expansion, and differentiation capacity, directly contributing to skeletal repair. Because Axin2 is a canonical Wnt-responsive gene, Axin2+ cells provide an important link between Wnt signaling, stem cell maintenance, and suture patency. However, the effects of Wnt signaling are context-dependent and may vary according to suture type, developmental stage, and cellular differentiation state. Therefore, Axin2+ cells should be interpreted as a Wnt-responsive SuSC population involved in maintaining the suture niche rather than as a simple indicator of increased or decreased osteogenesis.[18,20]

Prrx1+ cells, which constitute the regeneration-associated SuSC population, reside predominantly within the calvarial suture niche, decrease in number with age, and are distinct from pre-osteoblasts and mature osteoblasts. The experimental depletion of postnatal Prrx1+ cells impairs calvarial bone repair; however, their loss does not appear to cause major defects in normal postnatal calvarial development. These findings suggest that Prrx1+ cells play an important role in injury-responsive regeneration.[19,23]

In addition to lineage-associated markers, CD51+CD200+ skeletal stem/progenitor cells were prospectively isolated from cranial sutures by fluorescence-activated cell sorting. Their frequency decreased before the physiological fusion of the posterior frontal suture, whereas the patent sagittal and coronal sutures maintained a relatively stable proportion of these cells. A reduction or imbalance in CD51+CD200+ cells has also been observed in experimental models of syndromic and nonsyndromic CS. Canonical Wnt activation increases the representation of this population, and cotransplantation of CD51+CD200+ cells with Wnt3a prevents resynostosis after a suturectomy in Twist1+/- mice.[10]

In addition, BMPR1A+ cells provide a complementary view of SuSC biology. BMPR1A is both a cell-surface marker of human SuSCs and a functional regulator of their stemness, clonal expansion, and osteogenic capacity. SuSC-specific disruption of Bmpr1a in mice leads to premature differentiation, stem cell pool depletion, and suture midline–initiated CS, indicating that BMPR1A is required to maintain a patent suture niche.[16] Recent evidence supports a multistem cell model of calvarial homeostasis and pathological fusion. In Twist1-associated models, the depletion or dysfunction of cathepsin K-positive (Ctsk+) calvarial stem cells triggers the maladaptive expansion of discoidin domain receptor 2-positive calvarial stem cells and promotes pathological suture fusion, whereas the cotransplantation of Ctsk+ cells suppresses this phenotype. These findings suggest that CS arises from excessive osteogenic differentiation or SuSC depletion as well as an imbalance among functionally distinct stem cell populations.[24]

Collectively, available evidence indicates that SuSC populations differ in their niche localization, regenerative capacity, signaling responsiveness, and contribution to CS.

## 3. SuSC signaling pathway dysregulation in CS

SuSC activation and differentiation are closely related to the dysregulation of several signaling pathways. Among the pathways implicated in CS, the FGF, Wnt/β-catenin, and bone morphogenetic protein (BMP/BMPR1A–Hh) axes appear to play central roles in SuSC regulation. Addi-

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tional pathways, including Hippo/Yes-associated protein (YAP)-phosphoinositide 3-kinase (PI3K)-protein kinase B (AKT) signaling, Notch signaling, and receptor activator of nuclear factor-κB ligand (RANKL)-mediated remodeling further modify these core regulatory networks.

FGF signaling, mediated by FGFR1-4 tyrosine kinase receptors, plays a pivotal role in cranial development. Specifically, FGFR2 signaling is crucial for regulating stem cell proliferation within the suture, whereas FGFR1 primarily influences cranial bone formation by directing osteoblast differentiation.[25,26] Therefore, there are different pathological mechanisms of action in premature closure of the cranial suture due to FGFR1 and FGFR2 missense mutations. Ectopic activation of FGFR2 inhibits cell proliferation and depletes the bone progenitor cell pool, whereas excessive FGFR1 signaling promotes osteoblast differentiation. Both processes reduce the amount of unmineralized mesenchymal tissue within the suture and favor the premature fusion of adjacent cranial bones.[27] In addition, the complexity of FGF signaling in CS is further highlighted by its crosstalk with other proliferative pathways. For example, FGFR2 variants in dural cells may promote osteoblast proliferation and differentiation through Hippo/YAP–PI3K–AKT signaling, thereby providing a mechanism through which signals from neighboring tissues influence suture homeostasis.[28,29] Moreover, endogenous FGF/FGFR signaling can act upstream of BMP2 in cranial osteoblasts, while BMP2 activity is required for FGF2-induced late-stage osteogenic differentiation.[30]

Wnt signaling regulates osteoblast differentiation by stabilizing β-catenin and altering the expression of its downstream target genes. Within this network, Axin2 functions as a direct transcriptional target of β-catenin as well as a key negative feedback regulator of the pathway. Therefore, Wnt signaling links SuSC maintenance with lineage commitment and suture patency. However, the effects of Wnt signaling are context-dependent. They vary according to the developmental stage, suture location, and differentiation state of the responding cells. In an Apert syndrome mouse model, aberrant Wnt activation was associated with premature coronal suture fusion.[31] Conversely, other studies indicated that appropriately regulated canonical Wnt activity can support the maintenance or expansion of suture-resident skeletal stem/progenitor cells. Therefore, Wnt signaling should be interpreted as a regulatory axis whose imbalance, rather than uniform activation or inhibition, can contribute to CS.

BMP signaling is another central regulator of cranial suture homeostasis. SuSC-derived osteoprogenitor cells exhibit active BMP signaling and depend on BMP-mediated Hedgehog activity to coordinate their recruitment to osteogenic fronts. BMPR1A, a major receptor involved in BMP-SMAD signaling, is required to maintain SuSC properties and prevent premature differentiation. The disruption of BMPR1A-dependent regulation can disturb the balance between preservation of the central stem cell niche and osteogenic progression within the suture mesenchyme.[32] The hierarchical relationship between FGF and BMP is a key example of pathway crosstalk. BMP2 signaling is essential for FGF2-dependent induction of late osteogenic differentiation in cranial suture cells, and endogenous FGF/FGFR signaling acts as an upstream positive regulator of BMP2 in cranial osteoblasts.[30]

The Hh signaling pathway, which acts through Gli transcription factors, is essential for skeletal development and interacts closely with the BMP and Wnt pathways. Although Hh signaling is classically associated with endochondral ossification, it also contributes to regulating intramembranous bone formation in the calvarium. The partial restoration of suture morphology following Hh activation in Bmpr1a-mutant mice supports a functional BMP–Hh relationship in suture homeostasis.[32-34] Gli1+ cell abnormalities may disrupt both suture maintenance and the regenerative response.

Several additional pathways modify the activities of these core regulatory axes. IHH signaling may also synergize with RANKL, an osteoblast-derived paracrine factor that promotes osteoclast differentiation and resorptive activity, suggesting a potential link between suture cells and bone remodeling dynamics.[35] The Notch signaling pathway also contributes to the regulatory network of cranial development. Notch signaling influences cellular differentiation and proliferation within the suture mesenchyme by modulating target genes such as the HES family, MYC, and CDKN1A, and its dysregulation has been implicated in the pathogenesis of CS.[36]

Taken together, genetic variants and niche-derived signals converge on interconnected regulatory axes that determine whether SuSCs remain undifferentiated, proliferate, undergo lineage commitment, or progress toward osteogenic differentiation. FGF/FGFR, Wnt/β-catenin, and BMP/BMPR1A-Hh axes form the core framework, whereas Hippo/YAP-PI3K-AKT, Notch, and RANKL-mediated remodeling act as context-dependent modulators. The integrated model is shown in Fig. 3.

### 4. Environmental and biomechanical regulation of suture stem cell microenvironment

Although genetic alterations constitute the best-established etiological basis of CS, they do not fully explain its variable penetrance and phenotypic heterogeneity. Increasing evidence suggests that biomechanical, maternal,

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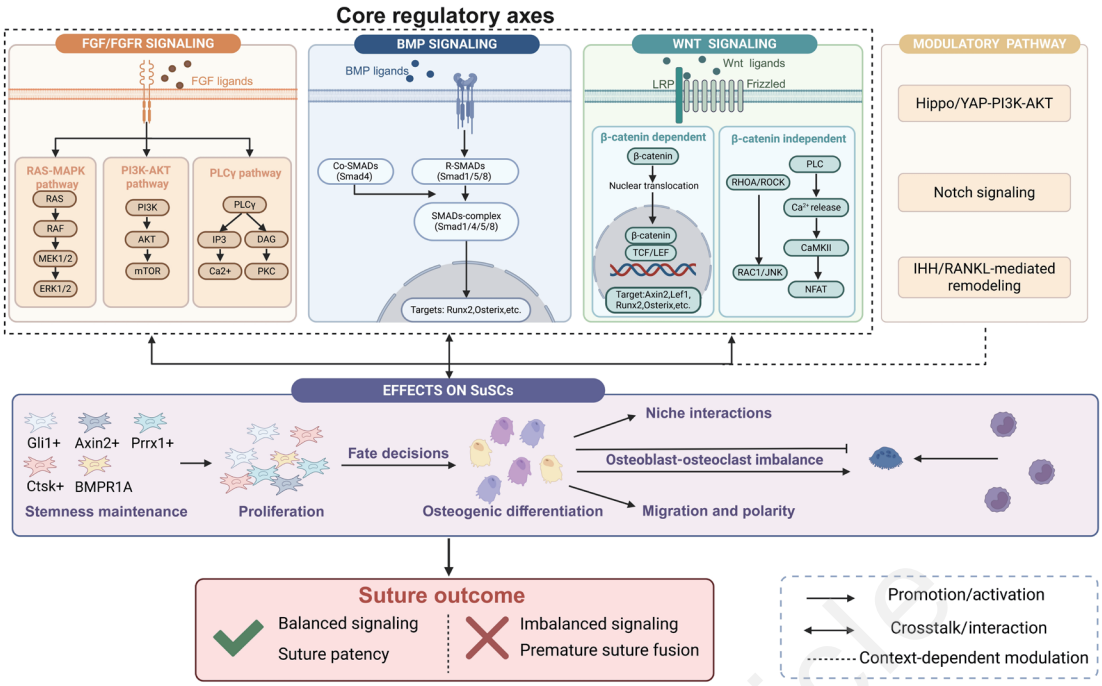



**Fig. 3.** Core signaling networks regulating suture mesenchymal stem cell fate in craniosynostosis. Suture homeostasis is governed by a complex interplay of major signaling pathways that regulate the behavior of SuSCs. The FGF/FGFR axis activates downstream cascades including PI3K-AKT, which collectively influences cell proliferation, survival, and differentiation. BMP signaling, through canonical Smad1/4/5/8, drives osteogenic differentiation by upregulating key transcription factors such as Runx2 and Osterix. Wnt signaling operates via both β-catenin-dependent and -independent mechanisms to modulate stemness, proliferation, and cytoskeletal dynamics. Additional modulatory inputs from Hippo/YAP, Notch, and other pathways further refine these signals. The integration of these pathways determines the fate of distinct SuSC populations (Gli1+, Axin2+, Prrx1+, Ctsk+), with balanced signaling maintaining suture patency, while imbalanced signaling promotes premature fusion. FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; RAS, rat sarcoma virus oncogene; MAPK, mitogen-activated protein kinase; RAF, rapidly accelerated fibrosarcoma; MEK1/2, mitogen-activated protein kinase kinase 1/2; ERK1/2, extracellular signal-regulated kinase 1/2; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; PLCγ, phospholipase C gamma; IP3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PKC, protein kinase C; BMP, bone morphogenetic protein; SMAD, Sma- and Mad-related protein; Co-SMAD, common-mediator SMAD; R-SMAD, receptor-regulated SMAD; Runx2, runt-related transcription factor 2; Wnt, wingless-related integration site; LRP, low-density lipoprotein receptor-related protein; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; Axin2+, axis inhibition protein 2-positive; Lef1, lymphoid enhancer-binding factor 1; RHOA, Ras homolog family member A; ROCK, Rho-associated coiled-coil-containing protein kinase; RAC1, Ras-related C3 botulinum toxin substrate 1; JNK, c-Jun N-terminal kinase; PLC, phospholipase C; CaMKII, calcium/calmodulin-dependent protein kinase II; NFAT, nuclear factor of activated T cells; YAP, Yes-associated protein; IHH, Indian hedgehog; RANKL, receptor activator of nuclear factor kappa-B ligand; SuSC, suture stem cell; Gli1+, glioma-associated oncogene homolog 1-positive; Prrx1+, postnatal paired related homeobox 1-positive; Ctsk+, cathepsin K-positive; BMPR1A, bone morphogenetic protein receptor type 1A.

endocrine, pharmacological, and environmental factors may modify susceptibility to premature suture fusion, although well-defined gene–environment interactions (G×E) remain incompletely established.[37,38] Rather than acting as independent causes, these factors may influence the developing suture microenvironment and interact with genetically determined molecules. Cranial sutures represent dynamic niches in which SuSCs, osteogenic progenitors, extracellular matrix, signaling pathways, and mechanical cues collectively maintain a balance between suture patency and osteogenesis.[14,39] This concept provides a potential framework through which genetic susceptibility and non-genetic influences may converge during SuSC homeostasis.

Among these factors, biomechanical regulation provides the strongest mechanistic link to SuSC behavior. Fetal constraints and altered mechanical loading have been associated with CS, while experimental studies have demonstrated that tensile forces directly regulate suture cell activity.[40-45] Gli1+ SuSCs are rapidly activated by mechanical expansion and contribute to subsequent bone remodeling; this response is accompanied by increased Wnt signaling, whereas β-catenin deletion markedly impairs force-induced SuSC activation and osteogenesis.[42] Mechanotransduction may also involve the Ras homolog family member A/Rho-associated protein kinase/transcription coactivator with PDZ-binding motif and insulin-like growth factor 1 pathways, which regulate

osteogenic differentiation, cellular contractility, and migration.[42-44] These findings suggest that mechanical signals can be translated into molecular responses that influence SuSC fate and suture remodeling. However, mechanical stimulation is also essential for physiological craniofacial growth and therapeutic distraction osteogenesis. Therefore, its effects depend on developmental stage, magnitude, duration, and cellular context.

Maternal, endocrine, pharmacological, and environmental exposures may provide an additional layer of regulation, although the available evidence is heterogeneous. Epidemiological studies have investigated maternal thyroid disease, smoking, selective serotonin reuptake inhibitors, occupational exposure, heavy metals, and other prenatal factors related to CS.[46-53] Experimental observations further suggest that exposure to thyroid hormones and Ni may influence osteogenic activity.[54,55] Nevertheless, associations have been inconsistent across studies, and potential confounding factors, such as maternal disease, medication indication, exposure intensity, and genetic background, limit causal interpretations. Therefore, these exposures should currently be considered potential modifiers of CS susceptibility rather than as established independent causes.

Importantly, emerging experimental evidence suggests that the genetic background may determine how the developing suture responds to external stimuli. Clinical observations involving an FGFR2 variant in the context of intrauterine cranial constraints, together with experimental studies combining Twist1 deficiency with thyroxine exposure, suggest that genetic background may modify the response of the developing suture to external stimuli, although well-defined additive G×E effects have not been consistently demonstrated.[39,40,54] Collectively, the current evidence supports a model in which genetic alterations establish susceptibility, whereas biomechanical and other non-genetic factors may modify the local suture environment and downstream cellular responses. Mechanistic evidence of the biomechanical regulation of SuSCs is currently the strongest, whereas the direct effects of environmental exposures on SuSC populations remain largely unexplored. Therefore, future studies should determine whether these factors alter SuSC self-renewal, migration, lineage commitment, or osteogenic differentiation in genetically susceptible backgrounds, thereby establishing whether the SuSC niche represents a convergence point between genetic and environmental regulation in pediatric patients with CS (Fig. 4).

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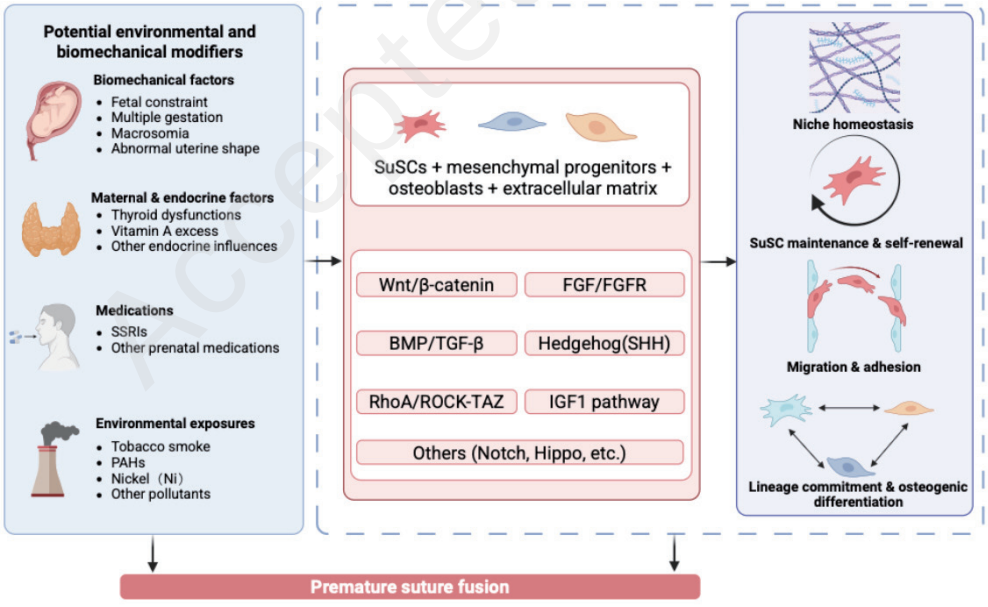



**Fig. 4.** Potential environmental and biomechanical modulation of suture stem cell homeostasis in craniosynostosis: Biomechanical, maternal and endocrine, medication-related, and environmental factors may influence the cranial suture niche and associated signaling pathways, thereby affecting SuSC maintenance, migration, adhesion, and lineage commitment. Dysregulation of these processes may contribute to premature suture fusion. BMP, bone morphogenetic protein; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; IGF1, insulin-like growth factor 1; PAHs, polycyclic aromatic hydrocarbons; RhoA/ROC–TAZ, Ras homolog family member A/Rho-associated protein kinase–transcription coactivator with PDZ-binding motif; SHH, sonic hedgehog; SSRIs, selective serotonin reuptake inhibitors; SuSCs, suture stem cells; TGF-β, transforming growth factor-beta

## Treatment

### 1. Clinical management of CS: Surgical treatment and adjunctive technologies

CS requires comprehensive treatment including surgery, medication-assisted treatment, rehabilitation training, psychological intervention, and regular review. Current guidelines recommend a multidisciplinary evaluation and individualized surgical planning based on age, affected suture, deformity severity, and syndromic status, with additional consideration of intracranial hypertension and airway or cranial volume compromise in complex cases.[56]

Surgery is the most commonly used and effective treatment option. The principal goals of surgical intervention are to release the fused sutures, expand intracranial volume, and improve cranial morphology. The optimal surgical approach depends on the affected sutures, age at diagnosis, deformity severity, and the presence of associated complications.[57] Endoscopic-assisted correction and open cranial vault reconstruction represent the 2 major surgical strategies for pediatric CS; each has distinct indications, advantages, and limitations. Endoscopic surgery is generally performed during early infancy, commonly at 2–4 months of age, and typically followed by postoperative helmet therapy to guide cranial remodeling during subsequent skull growth.[58-61] Compared to open reconstruction, endoscopic approaches are associated with shorter operative times, reduced blood loss and transfusion requirements, shorter hospital stays, and lower perioperative morbidity. Available evidence also suggests that satisfactory cranial morphological correction can be achieved with both approaches, although comparisons vary according to the involved suture, surgical technique, follow-up duration, and outcome measures.[58,61-63] In contrast, open cranial vault reconstruction is commonly performed later in infancy and provides immediate and more extensive correction of cranial morphology without the need for prolonged postoperative helmet therapy, offering greater flexibility for older infants and patients with more complex cranial deformities.[60,62-65] However, open procedures are generally associated with increased operative invasiveness, blood loss, transfusion requirements, and perioperative burden.

Current evidence has not established a consistent long-term neurodevelopmental advantage of endoscopic or open surgery, and further longitudinal comparative studies are required.[65,66] For patients with syndromic or multisuture CS, surgical management is often more complex, and cranial expansion may be required to address intracranial hypertension and provide adequate space for brain growth. Therefore, the choice between endoscopic and open surgery should not be considered a simple comparison of superiority but should be individualized according to patient age, affected sutures, deformity severity and complexity, associated intracranial or syndromic features, surgeon and center expertise, and postoperative helmet therapy feasibility. Postoperative residual deformities, skull defects, resynostosis, and the potential need for secondary procedures should also be considered during long-term follow-up.[57]

Advanced clinical technologies can improve surgical planning and precision. High-resolution 3-dimensional computed tomography, magnetic resonance imaging, virtual surgical planning, and 3-dimensional printing can be used to evaluate cranial morphology, compare surgical options, and generate patient-specific surgical templates. These approaches are currently used as clinical adjuncts rather than as independent biological treatments (Table 1).

### 2. Molecular and gene-based therapies

Given the limitations of traditional surgeries, emerging therapeutic strategies have attracted attention in recent years. Several molecular- and gene-based strategies have been investigated to elucidate the signaling mechanisms underlying CS.

Molecular therapies for CS aim to modulate the signaling abnormalities that promote premature suture fusion. Aberrant FGFR signaling is a major driver of several syndromic forms of CS, and small-molecule FGFR inhibitors, including ARQ087, are candidate compounds to suppress excessive FGFR activity. However, their efficacy

**Table 1. Comparison of endoscopic-assisted surgery and open cranial vault reconstruction for craniosynostosis**

| Clinical consideration | Endoscopic-assisted surgery | Open cranial vault reconstruction |
|---|---|---|
| Typical timing | Early infancy, commonly ~2–4 mo | Generally later in infancy; timing individualized |
| Surgical burden | Less invasive; generally less blood loss and shorter hospitalization | More invasive; generally greater blood loss and perioperative burden |
| Cranial remodeling | Gradual correction relying on subsequent skull growth | Immediate and more extensive cranial reshaping |
| Postoperative helmet therapy | Usually required | Generally not required |
| Patient selection | Best suited to appropriately selected younger infants; age window is relatively limited | Greater flexibility for older infants and complex cranial deformities |
| Key consideration | Lower perioperative burden but dependent on early diagnosis and helmet adherence | Greater reconstructive flexibility but at the cost of greater operative burden |

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and safety in CS-specific models remain insufficiently established, and systemic FGFR inhibition may interfere with normal skeletal growth and the development of other tissues.[27,67-69] In TWIST1-related CS, epigenetic modulation is another potential strategy. The pharmacological inhibition of KDM6A and KDM6B with GSK-J4 suppresses excessive osteogenic differentiation and helps maintain suture patency in Twist1-deficient mice, suggesting that epigenetic intervention may partially restore the balance between stem/progenitor cell maintenance and osteogenic commitment.[21,22] C-ROS-1 has also emerged as a potential molecular target. A recent preclinical study evaluated the controlled local release of crizotinib, a C-ROS-1 inhibitor, to suppress premature suture fusion. Localized delivery is particularly relevant because it may limit systemic exposure while maintaining therapeutic concentrations in the affected sutures.[70] However, this strategy remains experimental and has not yet been validated in clinical studies. Gene-based therapies provide an upstream approach by directly reducing pathogenic variant activity. In an Apert syndrome mouse model, adeno-associated virus serotype 9-mediated RNA interference against mutant Fgfr2 alleles attenuated premature coronal suture closure and improved abnormal calvarial phenotypes.[71] Although these findings provide proof of concept, gene-based therapies remain at the preclinical stage. Their clinical translation requires careful evaluation of the delivery efficiency, tissue specificity, off-target effects, and vector-associated immune responses as well as an optimal developmental window for intervention.

### 3. Stem cell-based and biomaterial-assisted regenerative therapies

The identification of SuSCs has created a new framework for regenerative therapy for CS. Conventional surgeries do not necessarily restore the biological niche required for sustained suture patency. As discussed above, a functional cranial suture depends on preservation of the stem/progenitor cell pool within the central suture mesenchyme and controlled osteogenic differentiation at the adjacent bone fronts. Therefore, the aim of

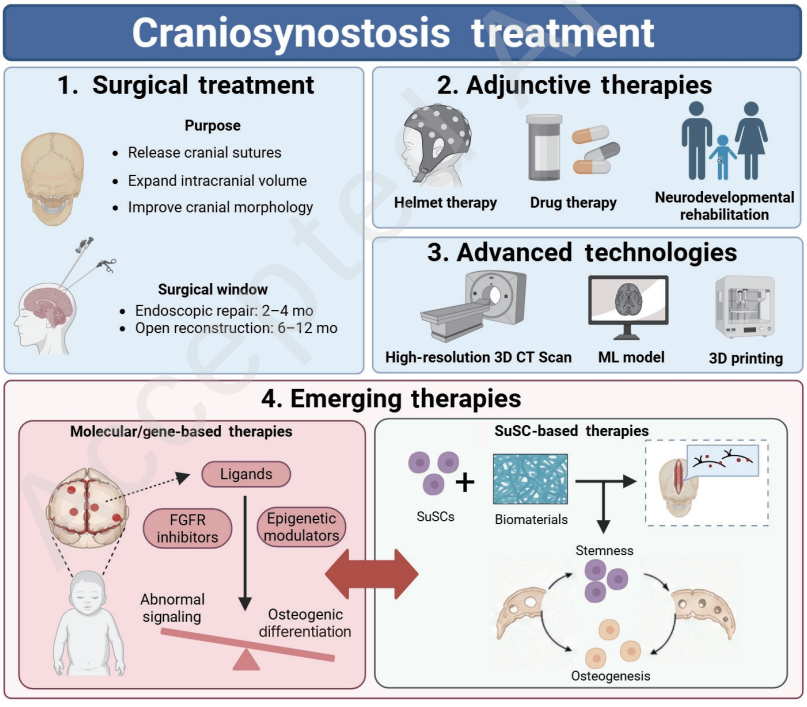



**Fig. 5.** Treatment for craniosynostosis. The management of craniosynostosis encompasses a spectrum of approaches ranging from established surgical interventions to emerging molecular therapies. Surgical treatment remains the cornerstone of treatment, with the primary goals of releasing fused sutures, expanding intracranial volume, and correcting cranial morphology. Adjunctive therapies, including helmet molding, drug therapy, and neurodevelopmental rehabilitation, complement surgical outcomes, are supported by advanced technologies. Emerging therapies target underlying pathophysiology, including SuSC-based regenerative approaches utilizing biomaterials to modulate stemness and osteogenesis as well as molecular/gene-based strategies that employ ligands or inhibitors to correct aberrant signaling pathways driving premature suture fusion. 3D, 3-dimensional; CT, computed tomography; ML, machine learning; FGFR, fibroblast growth factor receptor; SuSCs, suture stem cells.

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**Table 2. Diagnostic and therapeutic advances in craniosynostosis**

| Categorization | Key points | References |
|---|---|---|
| Preoperative evaluation and planning | | |
| Imaging & 3D anthropometry | Ultrasound as a primary radiation-free screening tool | 74) |
| | Impact of preoperative CT on surgical planning | 75) |
| | Crucial role of preoperative CT in surgical planning | 76) |
| | Limitations of cephalic index in severity assessment | 77) |
| | 3D photography as a radiation-free alternative to CT | 78) |
| | Validation of 3D morphometric indices for diagnosis | 79) |
| | Intraoperative 3D scanning for reconstruction guidance | 80) |
| Virtual surgical planning & 3D printing | VSP and 3D-printed guides for improved precision and reduced operative time | 81) |
| | High precision translation of VSP via optical navigation | 82) |
| | Superior deformity correction and reduced blood loss via VSP and 3D guides | 83) |
| | Integration of 3D simulation and biomechanical analysis for surgical optimization | 84) |
| | Preoperative CT reverse engineering for bone thickness assessment and complication avoidance | 85) |
| Surgical risk & comorbidity assessment | | |
| | Utilizes novel temporalis muscle and fat pad morphomic analyses to aid in the preoperative risk assessment and clinical prognosis of nonsyndromic craniosynostosis. | 86) |
| Functional evaluations | | |
| Ophthalmology/vision | SD-OCT provides a noninvasive, quantitative alternative for evaluating intracranial pressure. | 87) |
| Airway | Baseline neurocognitive development should be evaluated before and after surgery using formal scales. | 88) |
| Neurodevelopment | Cranial vault remodeling provides no significant evidence of altering lower neurodevelopmental trajectories. | 89) |
| | Mild cognitive delays may persist postoperatively, highlighting the need for overall neurodevelopmental tracking. | 90) |
| | Nonsyndromic craniosynostosis inherently carries a risk of neurodevelopmental delay, with both treated and untreated patients scoring lower than normal norms. | 91) |
| | Female gender, lack of insurance, and open surgery are risk factors for elevated caregiver stress, highlighting the need for psychological interventions. | 92) |
| Intraoperative surgical methods and techniques | | |
| Choice of core surgical modalities | Both endoscopic and traditional surgical techniques effectively normalize head shape, though they exhibit differences in the regional distribution of volumetric gains. | 93) |
| | The type of affected suture predicts the required duration of postoperative helmeting therapy, with metopic cases requiring longer treatment than sagittal cases. | 94) |
| | One-piece fronto-orbital distraction improves cranial morphology and volume in metopic craniosynostosis. | 95) |
| Specific vault remodeling & distraction techniques | Although midface distraction improves intracranial and airway volumes, failures to reach expected central midface advancement highlight the need for vector modifications. | 96) |
| | Rigid external distraction achieves significantly greater midface advancement compared to classic bone wiring or plate fixation, with stable long-term results across all methods. | 97) |
| | Specific intraoperative strategies, such as moderate overcorrection, significantly reduce the long-term risk of aesthetic defects associated with traditional fronto-orbital advancement. | 98) |
| | Posterior expansion via distraction osteogenesis is more effective at increasing intracranial volume than traditional fronto-orbital advancement for multisuture cases. | 99) |
| | Introduces a novel distraction osteogenesis technique to safely expand the posterior fossa in Chiari I malformation while minimizing cerebellar ptosis risk. | 100) |
| | Monobloc distraction effectively improves the upper midface but causes an anteroinferior rotation, leaving the lower midface insufficiently advanced. | |
| | Combined occipital and fronto-orbital distraction enables whole cranial vault expansion in syndromic craniosynostosis. | 101) |
| Osteotomy tools & fixation devices | Suture fixation yields similar clinical outcomes to absorbable plates but is associated with lower blood transfusion needs and earlier hospital discharge. | 102) |
| | Absorbable plates placed after strip craniectomy prevent early bone reossification and promote normal bone formation, helping high-risk infants avoid secondary surgeries. | 103) |
| | Piezoosteotomy is a less traumatic tool that significantly reduces postoperative red blood cell transfusion rates and the incidence of dural tears. | 104) |
| | Explores the intraoperative combined use of acute normovolemic hemodilution and erythropoietin to reduce allogeneic blood transfusion requirements. | 105) |
| Intraoperative blood management | Preoperative CT measurements of frontal and parietal bone thickness are associated with and can predict perioperative bleeding and transfusion needs. | 106) |

3D, 3-dimensional; CT, computed tomography; VSP, virtual surgical planning; SD-OCT, spectral-domain optical coherence tomography.

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regenerative therapy is not only to promote bone formation but to reconstruct a functional bone-suture-bone interface while reducing the risk of resynostosis.

In Twist1+/- mice, the implantation of SMSCs combined with a biodegradable material regenerated a functional cranial suture, corrected the skull deformity, normalized the intracranial pressure, and improved neurocognitive abnormalities.[22] A complementary strategy is based on the use of CD51+CD200+ suture-resident skeletal stem/progenitor cells. In Twist1+/- mice, the cotransplantation of CD51+CD200+ cells with Wnt3a after a suturectomy prevented resynostosis, linking the Wnt-responsive stem cell program described above with a potential regenerative intervention.[10]

Biomaterials may further improve regeneration by recreating the spatial organization of the native suture niche. Recent studies explored scaffolds designed to preserve stemness within a central suture-like region while supporting controlled osteogenic differentiation in adjacent bone compartments. A multicompartment biodegradable scaffold can maintain central stemness and promote osteogenic differentiation in the surrounding regions, thereby reproducing key features of the native interface in a mouse model of CS.[72] Li et al.[17] showed that injury-induced CXCL12–CXCR4 signaling promotes SuSC proliferation and directional migration toward calvarial defects and induces SHH and IHH production, which further supports SuSC expansion and osteoblastic differentiation. These findings suggest that future biomaterials may recruit endogenous SuSCs through the localized and temporally controlled delivery of niche-regulating factors.

Together, these studies demonstrate that stem cell-based treatment can be directly informed by SuSC biology: cell transplantation may restore depleted or imbalanced stem/progenitor cell populations, biomaterials may reconstruct the spatial organization of the niche, and injury-responsive signals may recruit endogenous SuSCs. However, all of these approaches remain preclinical. Their clinical translation requires careful evaluation of the cell source, immune compatibility, long-term safety, biomaterial integration, manufacturing reproducibility, and regulatory feasibility (Fig. 5; Table 2).

## Discussion

CS is a complex congenital disorder involving interactions between genetic alterations, environmental factors, and dysregulated signaling networks. However, CS should not be understood solely as a genetic disorder or consequence of excessive osteogenesis. Increasing evidence indicates that premature suture fusion is associated with impaired self-renewal, abnormal lineage commitment, SuSC population depletions or imbalances, and the disruption of local niches. FGF/FGFR, Wnt/β-catenin, and BMP/BMPR1A-Hh axes interact to regulate SuSC proliferation, differentiation, and maintenance, while additional pathways, including Hippo/YAP-PI3K-AKT, Notch, and RANKL-mediated remodeling, modulate these core networks. However, the spatial and temporal interactions among these pathways and their relationships with environmental and biomechanical factors remain incompletely understood.

Because these biological abnormalities cannot yet be fully corrected, current clinical management strategies remain centered on surgery. Surgical treatment can release fused sutures, expand the intracranial volume, and improve cranial morphology; however, it does not directly restore the stem cell niche required for sustained suture patency. This limitation provides a rationale for the development of mechanism-guided molecular and regenerative strategies as potential adjuncts to structural correction.

Molecular approaches targeting dysregulated signaling pathways or pathogenic variants remain in the preclinical stage, including FGFR-directed inhibition, epigenetic modulation by GSK-J4, local inhibition of C-ROS-1 signaling, and RNA interference targeting of mutant FGFR2 alleles. However, their delivery, specificity, developmental timing, and long-term safety require further evaluation.[67]

Stem cell-based therapies also remain preclinical but have particular translational potential because they aim to regenerate a functional suture niche rather than merely promoting bone formation. Yu et al.[22] showed that MSCs combined with biodegradable materials regenerated functional cranial sutures and improved cranial morphology, intracranial pressure, and neurocognitive outcomes. Similarly, CD51+CD200+ suture-resident skeletal stem/progenitor cells combined with Wnt3a prevented resynostosis, whereas biomaterial-guided reconstruction of the bone-suture-bone interface and injury-responsive CXCL12–CXCR4 and SHH/IHH signaling may facilitate endogenous SuSC recruitment during calvarial repair.[17,72]

Despite these advances, substantial barriers remain before stem cell-based therapies are applied in clinical practice. Most evidence of SuSC-mediated regeneration was derived from preclinical animal models; however, the identity, heterogeneity, developmental dynamics, and regenerative capacity of human SuSC populations remain incompletely characterized. The optimal cell source remains undetermined. Autologous cells may reduce im-

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mune incompatibility but require reliable harvesting, expansion, and quality control, whereas allogeneic cells raise concerns regarding immune rejection and long-term engraftment. Moreover, ex vivo expansion may alter the cellular phenotype or regenerative capacity, further complicating the development of standardized cell products. Long-term safety must also be carefully evaluated, as poorly controlled differentiation or osteogenic signaling may cause ectopic ossification, recurrent synostosis, or abnormal craniofacial growth. The integration of biomaterials is a key challenge. An ideal scaffold should be biocompatible and biodegradable, preserve a relatively unmineralized central suture-like region, integrate with the adjacent bone, and exhibit reproducible mechanical properties and degradation kinetics. Finally, the feasibility of implementing these approaches within the early developmental window in which CS is typically treated remains uncertain. Because most patients are infants or young children, rigorous preclinical validation, standardized manufacturing, long-term safety assessments, ethical reviews, and regulatory oversight are essential before clinical translation can occur.[73]

Future studies should clarify SuSC heterogeneity and niche regulation through lineage tracing, single-cell sequencing, spatial transcriptomics, and functional validation. Regenerative strategies should prioritize localized and temporally controlled interventions that preserve the central stem/progenitor cell niche while permitting controlled osteogenesis at the adjacent bone fronts. Surgery will remain indispensable in the foreseeable future; therefore, the most realistic near-term role of regenerative strategies may be to complement rather than replace surgical treatment through molecular modulation, biomaterial-assisted niche reconstruction, or the recruitment of endogenous SuSCs to promote functional suture regeneration and reduce resynostosis.

## Conclusion

SuSCs are central to CS pathogenesis because disruption of their maintenance, population balance, lineage commitment, and osteogenic differentiation can contribute to premature suture fusion. Current treatment remains centered on surgery and postoperative management, whereas emerging molecular, gene-targeted, and stem cell-based strategies may provide complementary approaches for restoring suture patency and reducing resynostosis. Future research should focus on clarifying how injury-responsive niche signals influence repair using lineage tracing, single-cell sequencing, and spatial transcriptomics. Particular attention should also be given to the development of biomaterials that recreate the bone-suture-bone interface, identification of patients most likely to benefit from regenerative interventions, and long-term evaluation of safety, durability, and regulatory feasibility. These advances may provide more precise and biologically informed treatment strategies for CS.

## Footnotes

Supplementary materials: materials are available at https://doi.org/10.3345/cep.2026.02299.

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contribution: Fangxin Guo, substantially contributed to the conception and design of the review, drafted the initial manuscript and revised it critically for important intellectual content; Guodong Song, revised the manuscript for important intellectual content, approved the final version to be published.

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## References

1. Brah TK, Thind R, Abel DE. Craniosynostosis: clinical presentation, genetics, and prenatal diagnosis. Obstet Gynecol Surv 2020;75:636-44.
2. Jimenez DF, Moon HS. Endoscopic approaches to craniosynostosis. Atlas Oral Maxillofac Surg Clin North Am 2022;30:63-73.
3. Kajdic N, Spazzapan P, Velnar T. Craniosynostosis - recognition, clinical characteristics, and treatment. Bosn J Basic Med Sci 2018;18:110-6.
4. Yapijakis C, Pachis N, Sotiriadou T, Vaila C, Michopoulou V, Vassiliou S. Molecular mechanisms involved in craniosynostosis. In Vivo 2023;37:36-46.
5. Hersh DS, Hughes CD. Syndromic craniosynostosis: unique management considerations. Neurosurg Clin N Am 2022;33:105-12.
6. Fearon JA, Barrientos S, Ditthakasem K, Herbert M. Optic nerve atrophy in syndromic craniosynostosis. Plast Reconstr Surg 2022;150:381e-386e.
7. Maruyama T, Yu HI, Hsu W. Skeletal stem cell isolation from cranial suture mesenchyme and maintenance of stemness

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in culture. Bio Protoc 2022;12:e4339.
8. Pi HJ, Huang B, Yuan Q, Jing JJ. Neural regulation of mesenchymal stem cells in craniofacial bone: development, homeostasis and repair. Front Physiol 2024;15:1423539.
9. Farmer DT, Mlcochova H, Zhou Y, Koelling N, Wang G, Ashley N, et al. The developing mouse coronal suture at single-cell resolution. Nat Commun 2021;12:4797.
10. Menon S, Salhotra A, Shailendra S, Tevlin R, Ransom RC, Januszyk M, et al. Skeletal stem and progenitor cells maintain cranial suture patency and prevent craniosynostosis. Nat Commun 2021;12:4640.
11. Wilkie AOM, Johnson D, Wall SA. Clinical genetics of craniosynostosis. Curr Opin Pediatr 2017;29:622-8.
12. Goumenos A, Tsoutsou E, Traeger-Synodinos J, Petychakis D, Gavra M, Kolialexi A, et al. Two novel variants in the TCF12 gene identified in cases with craniosynostosis. Appl Clin Genet 2019;12:19-25.
13. Li B, Wang Y, Fan Y, Ouchi T, Zhao Z, Li L. Cranial suture mesenchymal stem cells: insights and advances. Biomolecules 2021;11:1129.
14. Zhao H, Feng J, Ho TV, Grimes W, Urata M, Chai Y. The suture provides a niche for mesenchymal stem cells of craniofacial bones. Nat Cell Biol 2015;17:386-96.
15. Kong L, Wang Y, Ji Y, Chen J, Cui J, Shen W. Isolation and characterization of human suture mesenchymal stem cells in vitro. Int J Stem Cells 2020;13:377-85.
16. Maruyama T, Stevens R, Boka A, DiRienzo L, Chang C, Yu HI, et al. BMPR1A maintains skeletal stem cell properties in craniofacial development and craniosynostosis. Sci Transl Med 2021;13:eabb4416.
17. Li B, Ouchi T, Liu J, Yang Y. Injury-induced niche factors Cxcl12 and Shh/Ihh coordinate suture stem cell activation during calvarial bone regeneration. Sci Signal 2025;18:eadw7107.
18. Maruyama T, Jeong J, Sheu TJ, Hsu W. Stem cells of the suture mesenchyme in craniofacial bone development, repair and regeneration. Nat Commun 2016;7:10526.
19. Wilk K, Yeh SA, Mortensen LJ, Ghaffarigarakani S, Lombardo CM, Bassir SH, et al. Postnatal calvarial skeletal stem cells expressing PRX1 reside exclusively in the calvarial sutures and are required for bone regeneration. Stem Cell Reports 2017;8:933-46.
20. Di Pietro L, Barba M, Prampolini C, Ceccariglia S, Frassanito P, Vita A, et al. GLI1 and AXIN2 are distinctive markers of human calvarial mesenchymal stromal cells in non-syndromic craniosynostosis. Int J Mol Sci 2020;21:4356.
21. Pribadi C, Camp E, Cakouros D, Anderson P, Glackin C, Gronthos S. Pharmacological targeting of KDM6A and KDM6B, as a novel therapeutic strategy for treating craniosynostosis in Saethre-Chotzen syndrome. Stem Cell Res Ther 2020;11:529.
22. Yu M, Ma L, Yuan Y, Ye X, Montagne A, He J, et al. Cranial suture regeneration mitigates skull and neurocognitive defects in craniosynostosis. Cell 2021;184:243-56.e18.
23. Tooze RS, Miller KA, Swagemakers SMA, Calpena E, McGowan SJ, Boute O, et al. Pathogenic variants in the paired-related homeobox 1 gene (PRRX1) cause craniosynostosis with incomplete penetrance. Genet Med 2023;25:100883.
24. Bok S, Yallowitz AR, Sun J, McCormick J, Cung M, Hu L, et al. A multi-stem cell basis for craniosynostosis and calvarial mineralization. Nature 2023;621:804-12.
25. Miraoui H, Oudina K, Petite H, Tanimoto Y, Moriyama K, Marie PJ. Fibroblast growth factor receptor 2 promotes osteogenic differentiation in mesenchymal cells via ERK1/2 and protein kinase C signaling. J Biol Chem 2009;284:4897-904.
26. Miraoui H, Marie PJ. Fibroblast growth factor receptor signaling crosstalk in skeletogenesis. Sci Signal 2010;3:re9.
27. Balek L, Gudernova I, Vesela I, Hampl M, Oralova V, Kunova Bosakova M, et al. ARQ 087 inhibits FGFR signaling and rescues aberrant cell proliferation and differentiation in experimental models of craniosynostoses and chondrodysplasias caused by activating mutations in FGFR1, FGFR2 and FGFR3. Bone 2017;105:57-66.
28. Dong XH, Zhang MZ, Lai CZ, Li CC, Du L, Song GD, et al. Dura cells in the etiopathogenesis of Crouzon syndrome: the effects of FGFR2 mutations in the dura cells on the proliferation of osteoblasts through the hippo/YAP mediated transcriptional regulation pathway. Am J Transl Res 2021;13:11255-70.
29. Kosty J, Vogel TW. Insights into the development of molecular therapies for craniosynostosis. Neurosurg Focus 2015;38:E2.
30. Jiang T, Ge S, Shim YH, Zhang C, Cao D. Bone morphogenetic protein is required for fibroblast growth factor 2-dependent later-stage osteoblastic differentiation in cranial suture cells. Int J Clin Exp Pathol 2015;8:2946-54.
31. Min Swe NM, Kobayashi Y, Kamimoto H, Moriyama K. Aberrantly activated Wnt/β-catenin pathway co-receptors LRP5 and LRP6 regulate osteoblast differentiation in the developing coronal sutures of an Apert syndrome (Fgfr2S252W/+) mouse model. Dev Dyn 2021;250:465-76.
32. Guo Y, Yuan Y, Wu L, Ho TV, Jing J, Sugii H, et al. BMP-IHH-mediated interplay between mesenchymal stem cells and osteoclasts supports calvarial bone homeostasis and repair. Bone Res 2018;6:30.
33. Pan H, Zhang H, Abraham P, Komatsu Y, Lyons K, Kaartinen V, et al. BmpR1A is a major type 1 BMP receptor for BMP-Smad signaling during skull development. Dev Biol 2017;429:260-70.
34. Xu R, Khan SK, Zhou T, Gao B, Zhou Y, Zhou X, et al. Gαs signaling controls intramembranous ossification during cranial bone development by regulating both Hedgehog and Wnt/β-catenin signaling. Bone Res 2018;6:33.
35. Shin HR, Kim BS, Kim HJ, Yoon H, Kim WJ, Choi JY, et al. Excessive osteoclast activation by osteoblast paracrine factor RANKL is a major cause of the abnormal long bone phenotype in Apert syndrome model mice. J Cell Physiol 2022;237:2155-68.
36. Pakvasa M, Haravu P, Boachie-Mensah M, Jones A, Coalson E, Liao J, et al. Notch signaling: its essential roles in bone and craniofacial development. Genes Dis 2020;8:8-24.
37. Herrera-Luis E, Benke K, Volk H, Ladd-Acosta C, Wojcik GL. Gene-environment interactions in human health. Nat Rev Genet 2024;25:768-84.
38. Thomas D. Gene--environment-wide association studies: emerging approaches. Nat Rev Genet 2010;11:259-72.

Accepted Article

39. Durham EL, Howie RN, Cray JJ. Gene/environment interactions in craniosynostosis: a brief review. Orthod Craniofac Res 2017;20 Suppl 1:8-11.
40. Sanchez-Lara PA, Carmichael SL, Graham JM Jr, Lammer EJ, Shaw GM, Ma C, et al. Fetal constraint as a potential risk factor for craniosynostosis. Am J Med Genet A 2010; 152A:394-400.
41. Roth DM, Souter K, Graf D. Craniofacial sutures: signaling centres integrating mechanosensation, cell signaling, and cell differentiation. Eur J Cell Biol 2022;101:151258.
42. Jing D, Chen Z, Men Y, Yi Y, Wang Y, Wang J, et al. Response of Gli1+ suture stem cells to mechanical force upon suture expansion. J Bone Miner Res 2022;37:1307-20.
43. Li W, Zhao J, Wang J, Sun L, Xu H, Sun W, et al. ROCK-TAZ signaling axis regulates mechanical tension-induced osteogenic differentiation of rat cranial sagittal suture mesenchymal stem cells. J Cell Physiol 2020;235:5972-84.
44. Ye J, Wang J, Zhao J, Xia M, Wang H, Sun L, et al. RhoA/ROCK-TAZ axis regulates bone formation within calvarial trans-sutural distraction osteogenesis. Cell Signal 2024;121: 111300.
45. Al-Rekabi Z, Wheeler MM, Leonard A, Fura AM, Juhlin I, Frazar C, et al. Activation of the IGF1 pathway mediates changes in cellular contractility and motility in single-suture craniosynostosis. J Cell Sci 2016;129:483-91.
46. Rasmussen SA, Yazdy MM, Carmichael SL, Jamieson DJ, Canfield MA, Honein MA. Maternal thyroid disease as a risk factor for craniosynostosis. Obstet Gynecol 2007; 110:369-77.
47. Carmichael SL, Ma C, Rasmussen SA, Honein MA, Lammer EJ, Shaw GM, et al. Craniosynostosis and maternal smoking. Birth Defects Res A Clin Mol Teratol 2008;82:78-85.
48. Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM; National Birth Defects Prevention Study. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med 2007;356:2684-92.
49. Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. N Engl J Med 2007;356:2675-83.
50. Bérard A, Zhao JP, Sheehy O. Sertraline use during pregnancy and the risk of major malformations. Am J Obstet Gynecol 2015;212:795.e1-795.e12.
51. Bérard A, Zhao JP, Sheehy O. Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec Pregnancy Cohort. BMJ Open 2017; 7:e013372.
52. O'Brien JL, Langlois PH, Lawson CC, Scheuerle A, Rocheleau CM, Waters MA, et al. Maternal occupational exposure to polycyclic aromatic hydrocarbons and craniosynostosis among offspring in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2016;106:55-60.
53. Kielb C, Lin S, Herdt-Losavio M, Bell E, Chapman B, Rocheleau CM, et al. Maternal periconceptional occupational exposure to pesticides and selected musculoskeletal birth defects. Int J Hyg Environ Health 2014;217:248-54.
54. Durham EL, Howie RN, Black L, Bennfors G, Parsons TE, Elsalanty M, et al. Effects of thyroxine exposure on the Twist 1 +/- phenotype: a test of gene-environment interaction modeling for craniosynostosis. Birth Defects Res A Clin Mol Teratol 2016;106:803-13.
55. Xu C, Xu J, Zhang X, Xu S, Liu Q, Weng Z, et al. Serum nickel is associated with craniosynostosis risk: evidence from humans and mice. Environ Int 2021;146:106289.
56. Mathijssen IMJ; Working Group Guideline Craniosynostosis. Updated guideline on treatment and management of craniosynostosis. J Craniofac Surg 2021;32:371-450.
57. Xue AS, Buchanan EP, Hollier LH Jr. Update in management of craniosynostosis. Plast Reconstr Surg 2022;149: 1209e-1223e.
58. De Nigris Vasconcellos F, Garcia-Torrico F, Cardoso Betta VH, Marques Dias Pedroso G, de Almeida Tomas BE, Salolin Vargas VP, et al. Evaluating surgical techniques for craniosynostosis: a systematic review and meta-analysis on endoscopic approach versus open surgery. Neurosurgery 2025;97:766-79.
59. Ortega-Ruiz OR, Torres-Martínez M, Villafranca-Cantú M, Ávila-Cañedo RA, Piñeyro-Cantú E, Menchaca-Welsh E, et al. Open versus endoscopic surgery with helmet molding therapy in nonsyndromic patients with craniosynostosis: an updated systematic review and meta-analysis of clinical outcomes and treatment-related costs. Childs Nerv Syst 2024;41:53.
60. Goyal A, Lu VM, Yolcu YU, Elminawy M, Daniels DJ. Endoscopic versus open approach in craniosynostosis repair: a systematic review and meta-analysis of perioperative outcomes. Childs Nerv Syst 2018;34:1627-37.
61. Palavani LB, Costa M, Banderali I, Zattar Ribeiro PV, Nogueira BV, Belfort Santos M, et al. Endoscopic versus open treatment for sagittal craniosynostosis: a systematic review and meta-analysis. Neurosurg Rev 2025;48:262.
62. Duan J, Yang B. Clinical reference strategy for the selection of surgical treatment for nonsyndromic sagittal craniosynostosis: a systematic review and network meta-analysis. J Craniofac Surg 2025;36:536-41.
63. Yan H, Abel TJ, Alotaibi NM, Anderson M, Niazi TN, Weil AG, et al. A systematic review and meta-analysis of endoscopic versus open treatment of craniosynostosis. Part 1: the sagittal suture. J Neurosurg Pediatr 2018;22:352-60.
64. Yan H, Abel TJ, Alotaibi NM, Anderson M, Niazi TN, Weil AG, et al. A systematic review of endoscopic versus open treatment of craniosynostosis. Part 2: the nonsagittal single sutures. J Neurosurg Pediatr 2018;22:361-8.
65. Paliwoda ED, Patel IS, Horne MJ, Awad AN, Shihadeh H, Rudolph C, et al. Neurodevelopmental outcomes following open and endoscopic repair of isolated sagittal, coronal, metopic, and lambdoid craniosynostosis. Ann Plast Surg 2026;96(Suppl 5):S370-4.
66. Magge SN, Fotouhi AR, Allhusen V, Collett BR, Skolnick GB, Naidoo SD, et al. Cognitive outcomes of children with sagittal craniosynostosis treated with either endoscopic or open calvarial vault surgery. JAMA Netw Open 2024;7: e248762.
67. Al-Namnam NM, Jayash SN, Hariri F, Rahman ZAA, Alshawsh MA. Insights and future directions of potential genetic therapy for Apert syndrome: a systematic review. Gene Ther 2021;28:620-33.

Accepted Article

68. Barik M, Bano R, Bajpai M, Tripathy M, Das S, Dwivedi S. Novel mutation detection in craniosynostosis promotes characterization, identification, gene expression, tissue engineering and helps clinical practice and translational research. Neurol India 2020;68:435-9.
69. Camp E, Anderson PJ, Zannettino ACW, Glackin CA, Gronthos S. Tyrosine kinase receptor c-ros-oncogene 1 inhibition alleviates aberrant bone formation of TWIST-1 haploinsufficient calvarial cells from Saethre-Chotzen syndrome patients. J Cell Physiol 2018;233:7320-32.
70. Camp E, Garcia LG, Pribadi C, Paton S, Vasilev K, Anderson P, et al. Targeting of C-ROS-1 activity using a controlled release carrier to treat craniosynostosis in a preclinical model of Saethre-Chotzen syndrome. J Tissue Eng Regen Med 2024;2024:8863925.
71. Luo F, Xie Y, Wang Z, Huang J, Tan Q, Sun X, et al. Adeno-associated virus-mediated RNAi against mutant alleles attenuates abnormal calvarial phenotypes in an Apert syndrome mouse model. Mol Ther Nucleic Acids 2018;13: 291-302.
72. Swanson WB, Douglas L, Woodbury SM, Albright J, Pan H, Omi-Sugihara M, et al. A tissue engineering approach to regenerate the cranial suture skeletal stem cell niche with a multicompartment biomaterial scaffold. Bone Res 2026;14:58.
73. Lovell-Badge R, Anthony E, Barker RA, Bubela T, Brivanlou AH, Carpenter M, et al. ISSCR guidelines for stem cell research and clinical translation: the 2021 update. Stem Cell Reports 2021;16:1398-408.
74. Simanovsky N, Hiller N, Koplewitz B, Rozovsky K. Effectiveness of ultrasonographic evaluation of the cranial sutures in children with suspected craniosynostosis. Eur Radiol 2009;19:687-92.
75. Ranganathan K, Rampazzo A, Hashmi A, Muraszko K, Strahle J, Vercler CJ, et al. The role of preoperative imaging in the management of nonsyndromic lambdoid craniosynostosis. J Craniofac Surg 2018;29:36-9.
76. Ulma RM, Ranganathan KL, Vercler CJ, Garton HJL, Maher CO, Muraszko KM, et al. Weighing in on the controversy: preoperative imaging in unicoronal craniosynostosis leads to strategic changes in surgical care. Plast Reconstr Surg 2021;147:1133-9.
77. Derderian CA, Hallac R, Kane AA. An appraisal of the cephalic index in sagittal craniosynostosis, and the unseen third dimension. Plast Reconstr Surg 2018;141:459e.
78. Bruce MK, Tao W, Beiriger J, Christensen C, Pfaff MJ, Whitaker R, et al. 3D photography to quantify the severity of metopic craniosynostosis. Cleft Palate Craniofac J 2023; 60:971-9.
79. Skadorwa T, Wierzbieniec O, Podkowa K, Sośnicka K. The validation of morphometric outcomes and stratification system for nonsyndromic sagittal craniosynostosis following total calvarial remodeling. J Craniomaxillofac Surg 2024;52:1148-54.
80. García-Mato D, García-Sevilla M, Porras AR, Ochandiano S, Darriba-Allés JV, García-Leal R, et al. Three-dimensional photography for intraoperative morphometric analysis in metopic craniosynostosis surgery. Int J Comput Assist Radiol Surg 2021;16:277-87.
81. Almeida MN, Alper DP, Williams MCG, Ihnat JMH, Parikh N, Diluna M, et al. Virtual surgical planning in craniosynostosis reduces operative time and length of stay for cranial vault remodeling. J Craniofac Surg 2023;34:1931-3.
82. García-Mato D, Ochandiano S, García-Sevilla M, Navarro-Cuéllar C, Darriba-Allés JV, García-Leal R, et al. Craniosynostosis surgery: workflow based on virtual surgical planning, intraoperative navigation and 3D printed patient-specific guides and templates. Sci Rep 2019;9:17691.
83. Wu KL, Lu TC, Lin TC, Chan CS, Wu CT. Application of virtual planning and 3-dimensional printing guide in surgical management of craniosynostosis. World Neurosurg 2025;194:123475.
84. Li X, Zhu W, He J, Di F, Wang L, Li X, et al. Application of computer assisted three-dimensional simulation operation and biomechanics analysis in the treatment of sagittal craniosynostosis. J Clin Neurosci 2017;44:323-9.
85. Zanchi V, Volpe Y, Genitori L, Spinelli G. Software-assisted bone thickness evaluation in patients with syndromic craniosynostosis undergoing Le Fort III osteotomy: a technical note. Int J Oral Maxillofac Surg 2025;54:233-7.
86. Rinkinen J, Zhang P, Wang L, Enchakalody B, Terjimanian M, Holcomb S, et al. Novel temporalis muscle and fat pad morphomic analyses aids preoperative risk evaluation and outcome assessment in nonsyndromic craniosynostosis. J Craniofac Surg 2013;24:250-5.
87. Swanson JW, Aleman TS, Xu W, Ying GS, Pan W, Liu GT, et al. Evaluation of optical coherence tomography to detect elevated intracranial pressure in children. JAMA Ophthalmol 2017;135:320-8.
88. Lynn JV, Buchman LK, Breuler CJ, Buchman SR. Surgical timing and neurocognitive development among patients with craniosynostosis: analysis of confounders. Plast Reconstr Surg 2023;151:821-9.
89. Lynn JV, Buchman LK, Breuler CJ, Buchman SR. Longitudinal assessment of neurodevelopment in patients with nonsyndromic single-suture craniosynostosis: a retrospective review of 66 patients. J Craniofac Surg 2023;34:931-5.
90. Arnaud E. Discussion: American Society of Maxillofacial Surgeons Outcome Study: preoperative and postoperative neurodevelopmental findings in single-suture craniosynostosis. Plast Reconstr Surg 2004;114:848-9.
91. Da Costa AC, Anderson VA, Holmes AD, Lo P, Wray AC, Chong DK, et al. Longitudinal study of the neurodevelopmental characteristics of treated and untreated nonsyndromic craniosynostosis in infancy. Childs Nerv Syst 2013;29:985-95.
92. Tang AR, Chen JW, Sellyn GE, Chen H, Zhao S, Gannon SR, et al. Evaluating caregiver stress in craniosynostosis patients. J Neurosurg Pediatr 2022;30:224-31.
93. Calandrelli R, Pilato F, Massimi L, Panfili M, D'Apolito G, Gaudino S, et al. Quantitative evaluation of facial hypoplasia and airway obstruction in infants with syndromic craniosynostosis: relationship with skull base and splanchnocranium sutural pattern. Neuroradiology 2018;60:517-28.
94. Nguyen HT, Washington GN, Cepeda A Jr, Littlefield T, Teichgraeber JF, Greives MR, et al. Evaluation of helmeting therapy duration after endoscopic strip craniectomy for

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metopic and sagittal craniosynostosis. J Craniofac Surg 2024;35:415-8.
95. Fawzy HH, Choi JW, Ra YS. One-piece fronto-orbital distraction with midline splitting but without bandeau for metopic craniosynostosis: craniometric, volumetric, and morphologic evaluation. Ann Plast Surg 2019;83:285-92.
96. Landart M, Benichi S, James S, Arnaud É, Paternoster G, Khonsari RH. Frontal bone resorption after fronto-facial monobloc advancement in FGFR-related craniosynostoses: predictive factors. Plast Reconstr Surg 2025; 155:1027e-1035e.
97. Shetye PR, Davidson EH, Sorkin M, Grayson BH, McCarthy JG. Evaluation of three surgical techniques for advancement of the midface in growing children with syndromic craniosynostosis. Plast Reconstr Surg 2010;126:982-94.
98. Taylor JA, Paliga JT, Wes AM, Tahiri Y, Goldstein JA, Whitaker LA, et al. A critical evaluation of long-term aesthetic outcomes of fronto-orbital advancement and cranial vault remodeling in nonsyndromic unicoronal craniosynostosis. Plast Reconstr Surg 2015;135:220-31.
99. Kamil M, Oyoshi T, Komasaku S, Kuroki S, Higa N, Yoshimoto K. Fronto-orbital advancement and posterior cranial vault expansion using distraction osteogenesis in patients with multiple craniosynostosis. J Craniofac Surg 2021;32:1882-5.
100. Lu SM, Hazkour N, Atamian EK, Bradley J, Bastidas N. Inferiorly directed posterior cranial vault distraction for treatment of Chiari malformations. J Craniofac Surg 2023; 34:284-7.
101. Komuro Y, Shimizu A, Ueda A, Miyajima M, Nakanishi H, Arai H. Whole cranial vault expansion by continual occipital and fronto-orbital distraction in syndromic craniosynostosis. J Craniofac Surg 2011;22:269-72.
102. Sibar S, Karasu O, Erol G, Findikçioğlu K, Börcek AÖ. Comparison of the results of suture and resorbable plate-screw fixation in craniosynostosis. Ann Plast Surg 2022;89:385-90.
103. Sakahara D, Imai K, Masuoka T, Narita C, Matsumoto K, Kunihiro N. Novel suturectomy using absorbable plates in early surgery for craniosynostosis. J Craniofac Surg 2020; 31:e724-30.
104. Landes C, Vatter H, Marquardt G, Tran A, Quo F, Brand J, et al. Benefit of piezoosteotomy in cranioplasties for craniosynostosis correction versus conventional saw-and-chisel osteotomy: a pilot study. Cleft Palate Craniofac J 2015;52:287-92.
105. Meneghini L, Zadra N, Aneloni V, Metrangolo S, Faggin R, Giusti F. Erythropoietin therapy and acute preoperative normovolaemic haemodilution in infants undergoing craniosynostosis surgery. Paediatr Anaesth 2003;13:392-6.
106. Grove AM, Kirsch HM, Kurnik NM, Bristol RE, Sitzman TJ, Pfeifer C, et al. Preoperative frontal and parietal bone thickness assessment to predict blood loss and transfusion during extended suturectomy for isolated sagittal craniosynostosis. Cleft Palate Craniofac J 2025;62: 131-8.

**How to cite this article:** Guo F, Song G. Suture stem cells in pediatric craniosynostosis: pathophysiological mechanisms, surgical management, and emerging regenerative therapies. Clin Exp Pediatr [Epub ahead of print] https://doi.org/10.3345/cep.2026.02299

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