Facial Suture Pathology in Syndromic Craniosynostosis

Human and Animal Studies

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Background: Facial deformities in syndromic craniosynostosis are not only functionally, psychosocially, and aesthetically impairing but also notoriously challenging to reconstruct. Whether facial suture synostosis plays a significant role in the pathogenesis of these deformities is inadequately studied in human patients.

Methods: The MEDLINE database was queried using a methodologically generated search term inventory. Article inclusion was adjudicated by 2 authors after independent review. Articles provided insight into facial suture involvement in either syndromic craniosynostosis patients or animal models of disease.

Results: Comprehensive review yielded 19 relevant articles meeting inclusion criteria. Mid-20th century craniofacial biologists characterized how patent facial sutures are essential for normal postnatal facial development. They also posited that premature ossification disrupts growth vectors, causing significant dysmorphologies. Recently, facial suture synostosis was found to cause midfacial deformities independent of cranial base pathology in mouse models of syndromic craniosynostosis. Few recent studies have begun exploring facial suture involvement in patients, and although they have paved the way for future research, they bear significant limitations.

Conclusions: The hypothesis that facial suture synostosis acts in conjunction with cranial base pathology to produce the prominent, multifocal facial deformities in syndromic craniosynostosis may fundamentally alter surgical management and warrants further investigation. Methodically evaluating the literature, this review synthesizes all basic science and human clinical research thus far on the role of facial sutures in syndromic craniosynostosis and elucidates important topics for future research. We ultimately identify the need for rigorous imaging studies that longitudinally evaluate facial osteology across patients with various craniosynostosis syndromes.

Key Words: mice, humans, osteogenesis, osteology, MEDLINE, syndrome, craniosynostosis, skull base, models, sutures, craniofacial, plastic surgery, syndromic craniosynostosis, facial sutures, dysmorphologies, hypertelorism, exorbitism, synostosis, premature fusion, spheno-occipital synchondrosis, ossification, craniofacial malformations, Le Fort III, reconstructive surgery, suturectomy, pharmacologic FGFR inhibitors

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Facial sutures remain patent through at least adolescence and are essential for maintaining structural integrity of the face, absorbing mechanical stress, and facilitating postnatal osseous growth.[1–4] Syndromic cases, such as the *FGFR2*-related syndromes (Apert, Crouzon, and Pfeiffer), account for 15% to 30% of all craniosynostoses and involve several extracranial manifestations.[5] Coronal synostosis aside, these syndromes are notable for their prominent facial deformities causing functional, psychosocial, and aesthetic impairment.[6] Midfacial dysmorphism is the most ubiquitous, involving a retrusive and deformed maxilla that can cause airway compromise.[7–9] Hypertelorism and exorbitism can cause visual deficits, keratitis, or globe herniation.[5,9–11] Ears may be low set with surrounding bony deformities, causing conductive hearing loss.[5,9,12] Severe disfigurement with extensive childhood surgery is associated with deleterious psychosocial outcomes.[12,13]

Presently, the origin of these facial deformities is incompletely understood. They were initially considered sequelae of coronal synostosis; however, the discovery of premature ossification of cranial base synchondroses generated a new leading theory by the turn of the millennium.[7,14] The cranial base theory has eclipsed a third hypothesis—developed by early craniofacial experts and endorsed by present-day basic scientists—that premature fusion of facial sutures drives the development of facial deformities.[15–20]

Attaining a rigorous understanding of pathoetiology is critical for optimizing treatment. Facial manifestations are considerably challenging to reconstruct.[12] Incomplete knowledge about their cause(s) is a significant contributor to the frequently underwhelming aesthetic and functional outcomes of facial surgical interventions. This review synthesizes all findings from the basic science and clinical literature on the role of facial suture pathology in syndromic craniosynostosis. Leveraging these findings, we delineate future directions for clinical research that may enhance surgical management.

METHODS

A comprehensive MEDLINE search was performed to find all relevant studies published through September 2020. An inventory of search terms combining suture and craniosynostosis syndrome names and synonyms for "synostosis" was generated in a systematic fashion. Syntactical variations were deployed to extract all candidate articles, and ultimate inclusion was adjudicated by 2 authors. Articles included had to provide insight into facial suture development or pathology in either syndromic craniosynostosis patients or animal models of disease.

RESULTS

Comprehensive review yielded 19 articles strictly meeting inclusion criteria (Fig. 1). Articles date from 1976 to 2018. Of these, 6 and 13 involve human patients and transgenic mouse models, respectively. Among articles specific to humans, 2 are recent, in vivo, retrospective cohort imaging studies, and 4 are small sample reports published before 2000.

Facial Suture Pathology in Human Studies

Craniosynostosis syndromes were first characterized in Eugène Apert's 1906 description of children with syndactyly, acrocephaly, and markedly hypoplastic midfaces.[6] Crouzon syndrome was described in 1912.[6] These conditions were unique in simultaneously causing skull and facial deformities (Table 1). Craniofacial researchers who understood the importance of facial sutures in postnatal facial development

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19 All included studies

6 Human studies

2 Recent imaging studies

Author	Year	Type	Syndromes covered
Runyan et al.	2017	Retrospective cohort	Crouzon, Apert, Pfeiffer
Calandrelli et al.	2018	Retrospective cohort	Crouzon, Apert, Pfeiffer, Saethre-Chotzen

4 Early observational studies

Author	Year	Type	Syndromes covered
Kreiborg et al.	1976	Case report	Apert
Kreiborg	1981	Prospective case series	Crouzon
Kreiborg & Björk	1982	Case report	Crouzon
Persson	1995	Targeted review and discussion	Crouzon

13 Animal studies

Author	Year	Type	Syndromes covered
Wang et al.	2005	Transgenic mouse experiment	Apert
Twigg et al.	2009		Muenke
Martínez-Abadías et al.	2010		Apert
Purushothaman et al.	2011		Apert, Pfeiffer
Nah et al.	2012		Muenke
Hermann et al.	2012		Saethre-Chotzen
Martínez-Abadías et al.	2013		Apert
Liu et al.	2013		Crouzon, Pfeiffer
Martínez-Abadías et al.	2013		Crouzon, Pfeiffer
Motch Perrine et al.	2014		Apert
Parsons et al.	2014		Saethre-Chotzen
Holmes et al.	2018		Crouzon, Apert, Pfeiffer
Holmes et al.	2018		Crouzon, Pfeiffer

FIGURE 1. Articles yielded from comprehensive review focused on facial suture involvement in human patients and animal models of syndromic craniosynostosis.

became interested in whether pathology thereof could cause the facial deformities seen in these syndromes.

In his description of an 18-year-old postmortem Crouzon skull, Kreiborg and Björk[18] noted that "most sutures in the cranial base and face were prematurely fused." Orbital, nasal, maxillary, zygomaticotemporal, sphenozygomatic, frontosphenoidal, sphenosquamosal, and midpalatal sutures were all macroscopically obliterated, accompanied by significant facial skeletal deformities (Fig. 2). The maxilla was markedly hypoplastic, and the lateral orbital walls were laterally deviated. The authors attributed these bony findings to premature fusion of the maxillary sutures and sphenosquamosal/sphenozygomatic sutures, respectively. They highlighted that maxillary suture growth and bony remodeling of the maxilla are essential to postnatal midface development. The same authors also longitudinally followed craniofacial growth in a Crouzon patient using metallic jaw implants, finding inadequate maxillary lowering secondary to sutural growth interruption.[19] Significant maxillary narrowing corresponded to limited midpalatal suture growth. The overall maxillary deformity was attributed to "compensatory and dysplastic remodeling" as a physiologic response to stunted suture growth. Kreiborg et al's[29] report of a 22-month-old postmortem Apert skull noted premature fusion of the frontosphenoidal suture (Fig. 2). Bony findings included a hypoplastic maxilla and shallow orbits. The authors suggested that frontosphenoidal synostosis, with possible maxillary suture synostosis, contributed to the maxillary retrusion and growth retardation. The terms "faciostenosis" and "orbitostenosis" became routinely used to describe the facial skeletal deformities in Crouzon and Apert syndromes.[20,31]

The developing theory that facial suture synostosis is a primary pathology in craniosynostosis syndromes continued through the 1990s. Even by 1995, Persson[32] was characterizing how premature fusion causes maxillary hypoplasia in Crouzon. He postulated that while both calvarial and facial sutures fuse prematurely, calvarial synostosis is merely more apparent in early life. Synostotic facial sutures are obscured by a prolonged period of compensatory appositional growth, whereas analogous growth mechanisms of the neurocranium terminate earlier in infancy.

Although premature ossification of cranial base synchondroses in syndromic craniosynostosis had been recognized for decades, the degree to which it contributed to the craniofacial phenotype was uncertain until the elegant 1997 experiment by Rosenberg et al[33] demonstrated that cranial base pathology could alone generate significant facial deformities.[29,34,35] Compared with controls, rabbits with isolated surgical fusion of the spheno-occipital synchondrosis displayed reduced upper facial projection, a constricted nasopharynx, shallowed orbits, and a hypoplastic maxilla. Despite its lagomorphic nature, this study catalyzed a significant shift in human syndromic research focus from facial suture to cranial base pathology.[36–38]

Interest in facial suture involvement in craniosynostotic facial deformity experienced a notable renaissance with the Miri et al's[39] 2015 study of facial twist in unilateral coronal synostosis.[39] This phenotype involves midface deviation toward the synostosis, with lower face deviation toward the contralateral side. Reviewing the computed tomography (CT) images of 23 patients, the authors traced the development of facial twist to premature fusion of the frontomaxillary,

TABLE 1. Key Characteristics of 5 Major Craniosynostosis Syndromes, Including Craniofacial Deformities

		Apert	Crouzon	Pfeiffer	Muenke	Saethre-Chotzen
Genetic mutation[5,6,9]		Autosomal dominant mutation in *FGFR2* (66% S252W mutation, 32% P253R)	Autosomal dominant mutation in *FGFR2* (94% of cases)	Autosomal dominant mutation in *FGFR2* (94%) or *FGFR1* (<5%)	Autosomal dominant mutation in *FGFR3*	Autosomal dominant mutation in *TWIST1* (mesenchymal transcription factor)
Extracraniofacial manifestations[5,6,9]		Severe and symmetric syndactyly, variable intellectual disability	Normal extremities, rare intellectual disability	Broad, radially deviated thumbs, broad great toes, intellectual disability (types 2 and 3)	Brachydactyly, middle phalange deformity, coned epiphyses, carpal/tarsal fusions, rare intellectual disability	Mild syndactyly (sometimes), great toe deformity, short stature
Key craniofacial deformities[5,6,9]	**Neurocranial**	Bicoronal synostosis, turribrachycephaly, large anterior fontanelle	Coronal and other calvarial synostoses, brachycephaly	Brachycephaly (type 1 Pfeiffer), cloverleaf skull (type 2)	Uni or bicoronal synostosis	Uni or bicoronal synostosis
	Upper face/ears	Frontal flattening, exorbitism, hypertelorism, low-set ears	Tall forehead, frontal bossing, exorbitism, hypertelorism, auditory canal atresia	Severe exorbitism (types 2 and 3), hypertelorism, conductive hearing loss	Hypertelorism, downward angled palpebral fissures, exorbitism	Asymmetry, ptosis, hypertelorism, low hairline, low-set ears, small pinnae, conductive hearing loss
	Midface	Severe midface hypoplasia (possible airway compromise), low nasal bridge, nose beaking, possible cleft palate	Midface hypoplasia. Milder facial deformity than Apert	Midface hypoplasia (type 1), choanal stenosis, nose beaking	Mild midface hypoplasia, nose beaking	Asymmetry, rare maxillary hypoplasia, deviated septum
	Lower face		Mandibular prognathism			
Facial suture synostosis, by region	**Frontal**	Frontonasal[15] Frontomaxillary[16,21]	Frontonasal[22,23]	Frontonasal (later fusion than in Apert)[15]		
	Orbital	**Frontoethmoidal**[24,25]	**Sphenozygomatic**[18] **Frontoethmoidal**[24,25]	**Frontoethmoidal**[24,25]		
	Maxillary	Zygomaticomaxillary[16]	**Zygomaticomaxillary**[22–24]	**Zygomaticomaxillary**[24]	Zygomaticomaxillary[26,27]	
	Lateral		**Zygomaticotemporal**[18]		Zygomatic arch[26,27]	
	Nasal		**Internasal**[18]			
	Palatal	Maxillopalatine, premaxillary-maxillary[15]	**Midpalatal**[18]	Maxillopalatine, premaxillary-maxillary (later fusion than in Apert)[15]	Premaxillary-maxillary[26,27]	
	Mandibular					
	Basal	**Sphenoethmoidal**[24,25]	**Sphenoethmoidal**[24]	**Sphenoethmoidal**[25]	Spheno-occipital[26,27]	**Sphenoethmoidal**[24] Spheno occipital[28]
	Circummeatal	**Frontosphenoidal**[24,25,29] **Sphenoparietal, sphenosquamosal, parietomastoid, occipitomastoid**[24,25]	**Frontosphenoidal**[18,24] **Sphenoparietal, sphenosquamosal, parietomastoid**[24,25] **Occipitomastoid**[24,25,30] **Sphenosquamosal**[18]	**Frontosphenoidal, sphenoparietal, sphenosquamosal, parietomastoid, occipitomastoid**[24,25]		**Frontosphenoidal, sphenoparietal, parietomastoid**[24]

Facial suture synostoses reported in any animal or human studies are listed. Sutures in bold typeface are those found to be synostosed in human subjects.

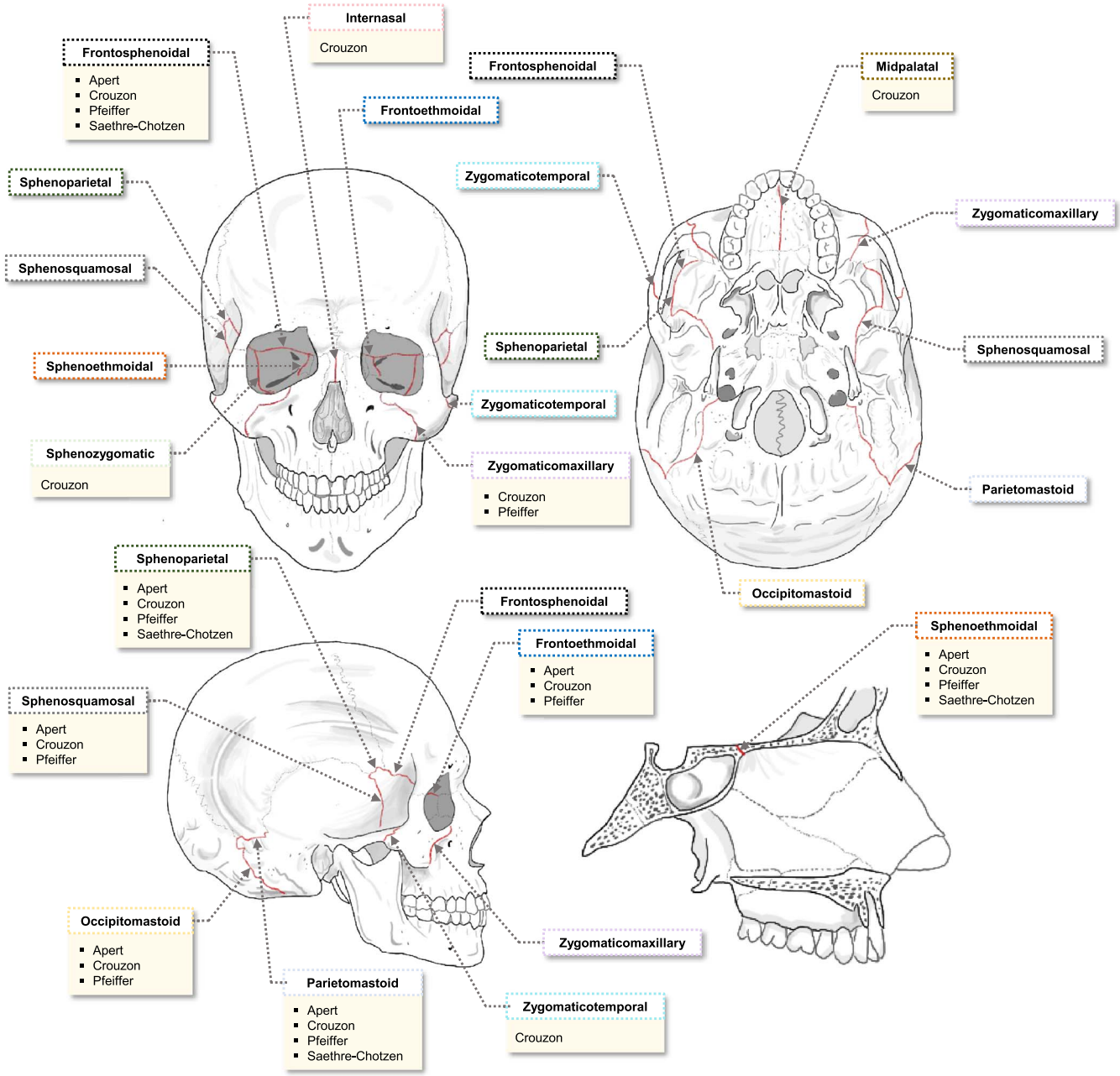

FIGURE 2. Craniofacial skeletal schematics illustrating the facial sutures documented to be prematurely fused in human cases of craniosynostosis syndromes. Four views are provided: anterior, lateral, inferior, and midline sagittal.

frontonasal, and nasomaxillary sutures on the synostotic side. Subsequently, facial suture involvement has been documented in other nonsyndromic craniosynostoses, such as metopic trigonocephaly.[40–42] Beyond metopic synostosis, premature fusions of the frontonasal, internasal, frontomaxillary, frontozygomatic, and frontoethmoidal have now all been reported.[40,41] Notably, frontonasal and internasal synostosis may exacerbate metopic angulation and indicate severe disease.[41]

To date, there is a dearth of analogous research in human syndromic craniosynostosis, despite promising findings in experimental animals as will be discussed. Literature review yielded only 2 groups—Calandrelli et al[24] and Runyan et al[25]—who have assessed facial region sutures on imaging of syndromic patients (Table 2). The study by Calandrelli et al[24] is the most comprehensive to date, examining a wide set of craniofacial sutures on the CT images of 19 preoperative syndromic infants (mean age, 206 days). They included 9 Crouzon, 4 Apert, 3 Pfeiffer, and 3 Saethre-Chotzen patients. They are the first and only to evaluate facial sutures located primarily within the viscerocranium, including the frontozygomatic, frontomaxillary, frontonasal, zygomaticotemporal, sphenozygomatic, zygomaticomaxillary, nasomaxillary, and internasal sutures. Likely because of the young age of the study

TABLE 2. Human Imaging Studies Evaluating Patency of Facial Region Sutures in Syndromic Craniosynostosis Patients

				Prematurely Fused Facial Sutures, by Region								
Study	**Strengths/Contributions**	**Limitations**	**Syndromes**	**Frontal**	**Orbital**	**Maxillary**	**Basal**	**Circummeatal**				
Runyan et al[25] (2017)	• First study to systematically evaluate patency of multiple craniofacial sutures in syndromic patients • Assessed multiple CT scans for each patient to achieve longitudinal survey (ie, monitored changes in suture patency over time) • Stratified degree of suture fusion (ie, partial versus complete)	• Only evaluated major/minor calvarial sutures and cranial base synchondroses. Although several minor sutures have a perifacial location, this study did not include sutures located primarily within the viscerocranium • Small sample size (n = 9)	Apert (n = 2)	M	FE		SE	FS	SP	SS	PM	OM
				50%	*100%*		*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
					100%		100%	100%	100%	0%	100%	0%
					8.6 mo		8.6 mo	8.6 mo	8.6 mo		8.6 mo	
			Crouzon (n = 3)		FE		SO	SP	SS	PM	OM	
					33%		*67%*	*33%*	*67%*	*67%*	*67%*	
					100%		100%	100%	50%	100%	50%	
					8.4 mo		2.3 mo	8.4 mo	5.4 mo	8.4 mo	8.4 mo	
			Pfeiffer (n = 4)	M	FE		SE	FS	SP	SS	PM	OM
				75%	*75%*		*75%*	*50%*	*100%*	*100%*	*100%*	*75%*
				2.8 mo	100%		100%	100%	100%	100%	100%	67%
					2.4 mo		6.9 mo	7.6 mo	2.4 mo	2.4 mo	2.4 mo	7.0 mo
Calandrelli et al[24] (2018)	• Most comprehensive clinical study to date evaluating craniofacial suture patency in syndromic craniosynostosis patients • Only study thus far to evaluate facial sutures located primarily within the viscerocranium	• Early, homogenous age of subjects at time of CT imaging (mean age, 206 d; likely precedes when most facial suture synostosis would be expected) • CT images analyzed were obtained at a single time point for each patient (ie, lack of longitudinal survey) • Small sample size (n = 19)	Apert (n = 4)	M			SE	FS	PM	OM	SP	SS
				50%			*50%*	*100%*	*100%*	*50%*	*50%*	*50%*
								0%	0%	0%	100%	0%
			Crouzon (n = 9)	M	FE	ZM	SE	FS	PM	OM	SP	SS
				11%	*11%*	*44%*	*11%*	*44%*	*100%*	*67%*	*56%*	*78%*
					100%	100%		25%	89%	100%	80%	71%
			Pfeiffer (n = 3)	M		ZM		FS	PM	OM	SP	SS
				33%		*33%*		*33%*	*33%*	*33%*	*67%*	*67%*
						100%		0%	100%	100%	100%	100%
			Saethre-Chotzen (n = 3)	M			SE	FS	PM	SP		
				67%			*67%*	*100%*	*67%*	*67%*		
								100%	100%	100%		

No synostosis of sutures in the lateral, nasal, palatal, or mandibular regions was characterized by these studies, so these regions are not included in this table.

FE, frontoethmoidal; FS, frontosphenoidal; M, metopic; OM, occipitomastoid; PM, parietomastoid; SE, sphenoethmoidal; SO, spheno-occipital; SP, sphenoparietal; SS, sphenosquamosal; ZM, zygomaticomaxillary.

Prevalence of synostosis.

Percentages in italics indicate prevalence of synostosis.

% of synostosis cases with bilateral involvement (if applicable).

Earliest age of complete fusion (if applicable).

cohort, viscerocranial sutures were all patent, except for premature fusion of the zygomaticomaxillary in 5 infants (4 Crouzon and 1 Pfeiffer; Fig. 2). The authors suggest that facial suture involvement, although rare this early in postnatal life, indicates heightened disease severity. They also hypothesize that premature fusion of maxillary sutures contributes to midface retrusion and exacerbates airway hypoplasia.

Despite its novel contribution to the field, their study is limited by the young, homogeneous age of the cohort and the lack of longitudinal tracking. The patients were studied at an age preceding both when premature facial suture fusion likely manifests and when rapid postnatal facial development occurs.[32,43] Without mitigating this drawback by tracking patients over time, the study very likely overlooks a significant degree of potential pathology. Longitudinal survey is, however, a noteworthy characteristic of a similar 2017 study by Runyan et al[25] of cranial base articulations in syndromic patients. Although their study did not include viscerocranial sutures located completely within the face, certain ones that they evaluated are relevant because of their perifacial location. The authors monitored suture closure progression by evaluating CT images over time—from ages of 0.1 to 18.6 months—in 9 patients (3 Crouzon, 2 Apert, and 4 Pfeiffer). They reported premature fusions of the sphenosquamosal, parietomastoid, sphenoparietal, frontoethmoidal, metopic, and frontosphenoidal sutures, as well as of the occipitomastoid, sphenoethmoidal, and spheno-occipital synchondroses (Fig. 2). Synostosis tended to occur initially within the cranial base but gradually extended superiorly to calvarium, suggesting that all craniofacial articulations should be thoroughly evaluated in patients with a syndromic facial phenotype but patent calvarial sutures.

Facial Suture Pathology in Animal Models

Mutant mouse models of craniosynostosis syndromes replicate key craniofacial deformities observed in human patients.[21,44] Histologic analyses confirm that the genetic modifications significantly alter cellular physiology at sutures.[45,46] Fidelity to human phenotype makes these models ideal for investigating the pathoetiology of facial deformities. Over the past decade, basic scientists have made key discoveries underscoring the role of facial suture involvement.

Crouzon syndrome, the most common, is associated with an autosomal dominant gain-of-function *FGFR2* mutation.[6] Patients present with bilateral coronal synostosis, brachycephaly, and various facial deformities (ie, midface retrusion, exorbitism, and hypertelorism; Table 1). Variable patterns of facial suture synostosis have been described in Crouzon mouse models (Table 3). Liu et al[49] documented premature fusion of the frontonasal, maxillopalatine, and zygomaticotemporal sutures in $Fgfr2^{C342Y/+}$ mutant mice, but others have found mainly the frontonasal and zygomaticomaxillary to be synostosed.[22,23] Interestingly, investigators attempted but failed to reverse craniofacial deformities by administering BMN 111, an inhibitor of FGFR signaling.[23] Although the drug enhanced endochondral long bone growth, it disappointingly had no effect on coronal or frontonasal suture synostosis or craniofacial dimensions.

Apert syndrome, characterized by bilateral coronal synostosis, midfacial dysmorphism, and syndactyly, is among the 3 most common syndromes (with Crouzon and Pfeiffer).[6] More than 98% of cases are caused by an autosomal dominant gain-of-function mutation in the *FGFR2* gene.[51] First characterized in 2005, facial suture synostosis in Apert $Fgfr2^{S252W/+}$ mice (the mutation in two thirds of human patients) was found to involve the frontopremaxillary, premaxillary-maxillary, frontonasal, and zygomaticotemporal sutures.[47] Mutant mice displayed ocular proptosis, brachycephaly, distorted maxillae, hypoplastic mandibles, and smaller faces and palates than wild-type littermates. The zygomaticomaxillary and premaxillary-maxillary sutures were found to be invariably synostosed in both $Fgfr2^{S252W/+}$ and $Fgfr2^{P253R/+}$ mice at birth.[17] These 2 mutations account for virtually all cases of human Apert syndrome. The severity of facial deformities, like posterior palatal displacement, was not strongly correlated with coronal suture patency and unlikely the sequelae of calvarial synostosis.

A murine study by Purushothaman et al[15] (2011), which demonstrated that facial suture synostosis could produce midfacial hypoplasia in the absence of cranial base pathology, was catalytic in generating research interest in facial sutures. A micro-CT image revealed premature fusion of the frontonasal, maxillopalatine, and premaxillary-maxillary sutures, with consequent deformity of the premaxilla, maxilla, and palatine bones in $Fgfr2^{S252W/+}$ mice. These anomalies were already present on the first postnatal day, when endochondral growth centers were unossified. Their findings substantiated that facial synostosis is a primary pathology in syndromic craniosynostosis that independently produces facial deformity. Quantitative cephalometry in the $Fgfr2^{S252W/+}$ and $Fgfr2^{P253R/+}$ models illuminated a strong positive correlation between the degree of premature facial suture fusion and severity of craniofacial deformities.[16]

Holmes et al[21] refined the link between facial synostosis and consequent local growth deficits. They found that the early timing of frontomaxillary synostosis precluded optimal mediolateral and dorsoventral expansion of the nasal capsule, predisposing these mice to airway hypoplasia. Another group found that the 2 Apert mutations confer a differential predilection for facial synostosis, resulting in variable severity of palatal deformities.[48] Compared with $Fgfr2^{P253R/+}$ littermates, $Fgfr2^{S252W/+}$ mice had more hypoplastic and distanced palatal shelves, fused maxillopalatine sutures, and abnormally developed interpremaxillary sutures. These manifestations are consistent with the finding that cleft palate is more common in Apert patients with the S252W mutation.

Investigators also highlight the heterogeneity in various mesenchymal cell responses to FGF ligands and receptor mutations. Martínez-Abadías et al[48] hypothesize that this is how different craniofacial sutures can exhibit variable patency under the influence of the same *FGFR* mutation.

Pfeiffer syndrome, mainly associated with an *FGFR2* mutation (and an *FGFR1* mutation in less than 5% of cases), is a multisutural craniosynostosis with a phenotypic spectrum.[6] Types 2 and 3 involve more severe craniofacial abnormalities, including exorbitism and cloverleaf skull (in type 2) than type 1. Purushothaman et al[15] also evaluated facial suture synostosis in the $Fgfr1^{P250R/+}$ Pfeiffer mouse model. Fusion patterns were generally similar to those of the Apert model, although synostosis was detected at a later time point. Cranial base growth centers were also unossified at the time that facial anomalies became apparent. The authors interpreted these findings to suggest that in early postnatal development, the $Fgfr1^{P250R/+}$ mutation renders less severe midfacial deformity compared with the Apert mutation.

Muenke syndrome, involving an autosomal dominant mutation in *FGFR3*, is characterized by coronal synostosis, mild midface hypoplasia, subtle finger and limb deformities, hearing loss, and rarely cognitive impairment.[6] The milder midface deformity in Muenke patients may be due to a lower level of *FGFR3* expression, compared with that of *FGFR1* and *FGFR2*, in human embryonic facial and cranial base mesenchyme.[36] Twigg et al[26] and Nah et al[27] characterized the $Fgfr3^{P244R/+}$ Muenke mouse model, which interestingly lacks coronal suture synostosis, but exhibits premature fusion of zygomaticomaxillary, premaxillary-maxillary, and zygomatic arch sutures. The zygomatic arch synostoses may contribute to a constrained orbit and exorbitism.[26] The mice also have maxillary retrusion associated with a short anterior cranial base and synostotic spheno-occipital synchondrosis.

Saethre-Chotzen syndrome, associated with an autosomal dominant mutation in *TWIST1* (a transcription factor expressed in early patent sutures), manifests as coronal synostosis, hypertelorism, maxillary hypoplasia, short stature, and frequently unaffected cognitive ability.[6] Although they did not assess facial sutures broadly, Hermann et al[28] characterized how the $Twist1^{+/-}$ mutation can simultaneously accelerate intramembranous and endochondral ossification at craniofacial sutures

TABLE 3. Murine Studies of Facial Suture Synostosis and Craniofacial Deformities in Syndromic Craniosynostosis

Study	Syndrome	Genetic Aberration	Craniofacial Deformities	Prematurely Fused Facial Sutures, by Region					Key Contributions
				Frontal	Maxillary	Lateral	Palatal	Basal	
Wang et al[47] (2005)	Apert	*FGFR2* (*Fgfr2*$^{S252W/+}$)	Ocular proptosis (from zygomatic arch disruption), brachycephaly, smaller facial and palatal bones than controls, deformed maxilla (large sinus in the frontal process, bowing of the medial wall, bowing of the zygomatic process, hypoplastic mandible)	FP, FN		ZT	PrMx		First to characterize facial suture synostosis in a mouse model of syndromic craniosynostosis
Twigg et al[26] (2009)	Muenke	*FGFR3* (*Fgfr3*$^{P244R/+}$)	Small and rounded skull, shortened and twisted snout, dental malocclusion, fused zygomatic arch		ZM	ZT	PrMx		First to develop a Muenke mouse model. Facial suture synostosis (ie, palatal, zygomatic sutures) was significantly more common than calvarial suture synostosis in this model
Martínez-Abadías et al[17] (2010)	Apert	*FGFR2* (*Fgfr2*$^{S252W/+}$ and *Fgfr2*$^{P253R/+}$)	Midface hypoplasia with posteriorly displaced palate, brachycephaly, inferiorly displaced cranial base		ZM		PrMx		Facial deformities are unlikely the sequelae of calvarial suture synostosis
Purushothaman et al[15] (2011)	Apert	*FGFR2* (*Fgfr2*$^{S252W/+}$)	Gross midfacial deformities, severe palatine bone dysplasia (anteriorly curved vertical process, overall porous appearance), deformed maxilla and premaxilla, widened intermaxillary suture	FP, FN			MxP, PrMx		Facial suture synostosis produces midfacial hypoplasia in the absence of cranial base pathology
	Pfeiffer	*FGFR1* (*Fgfr1*$^{P250R/+}$)	Gross midfacial deformities, severe palatine bone dysplasia (anteriorly curved vertical process), porous bone appearance (premaxilla, maxilla, palatine bones)	FP, FN			MxP, PrMx		*Fgfr1* (Pfeiffer) mutation confers similar, but milder craniofacial deficits and facial synostosis patterns as *Fgfr2* (Apert) mutation
Nah et al[27] (2012)	Muenke	*FGFR3* (*Fgfr3*$^{P244R/+}$)	Dome-shaped and shortened skull, snout deviation, hypoplastic premaxilla, incisor malocclusion				PrMx	SO, IS	Synostosis of facial sutures and cranial base synchondroses occurs more frequently than calvarial suture synostosis in Muenke mice
Hermann et al[28] (2012)	Saethre-Chotzen	*TWIST1* (*Twist1*$^{+/-}$)	Coronal suture fusion, patent metopic suture					SO	A single gene mutation can simultaneously disrupt different mesenchymal maturation processes occurring at various anatomic sites (ie, intramembranous ossification at a calvarial suture and endochondral ossification at a cranial base synchondrosis)

Continued next page

TABLE 3. *(Continued)*

Study	Syndrome	Genetic Aberration	Craniofacial Deformities	Prematurely Fused Facial Sutures, by Region					Key Contributions
				Frontal	Maxillary	Lateral	Palatal	Basal	
Martínez-Abadías et al[48] (2013)	Apert	*FGFR2* (*Fgfr2*$^{S252W/+}$ and *Fgfr2*$^{P253R/+}$)	*S252W* mice had more severe palatal deformities (smaller/more separated palatal shelves, more fusion of the maxillopalatine suture, more abnormally developed interpremaxillary suture) than *P253R* littermates				MxP, IP		Different mutations underlying a syndrome confer variable severities of facial suture synostosis and consequent deformity
Martínez-Abadías et al[22] (2013)	Crouzon (and Pfeiffer)	*FGFR2* (*Fgfr2c*$^{C342Y/+}$)	Shortened nasal bones, premaxilla, and palatal shelves; significantly reduced nasopharyngeal volume; taller and wider caudal face		ZM				Found fusion of only one major facial suture (in contrast to Liu et al[49]). Facial suture synostosis may be attenuated in Crouzon (relative to in Apert)
Liu et al[49] (2013)	Crouzon (and Pfeiffer)	*FGFR2* (*Fgfr2c*$^{C342Y/+}$)	Severe midface hypoplasia (shortened maxillary and nasal length), dome-shaped calvarium (increased cranial height and width, decreased length), shortened zygomatic arch, shortened anterior cranial base	FN		ZT	MxP		Documented the presence of facial suture synostosis in Crouzon mouse model
Motch Perrine et al[16] (2014)	Apert	*FGFR2* (*Fgfr2*$^{S252W/+}$ and *Fgfr2*$^{P253R/+}$)	Narrowed, flattened, and shortened facial skeleton; decreased rostrocaudal growth across the palatal shelves	FM	ZM		MxP, PrMx		Quantitatively demonstrated the strong positive correlation between the degree of facial suture synostosis and severity of craniofacial deformity
Parsons et al[50] (2014)	Saethre-Chotzen	*TWIST1* (*Twist1*$^{+/-}$)	Acrocephaly, brachycephaly, shortened cranial base, widened and shortened face						Facial deformities (especially nasal) in Saethre-Chotzen mice could be due to facial suture synostosis. A future "thorough examination of the facial sutures" in *Twist1* mutant mice is needed
Holmes et al[21] (2018)	Apert	*FGFR2* (*Fgfr2*$^{S252W/+}$ and *Fgfr2*$^{P253R/+}$)	Significantly reduced nasal passage volume, defective nasal septum (resulting in incompletely separated left and right nasal passages)	FM					Elucidated a mechanism by which a synostosed facial suture produces a local facial deformity
	Crouzon (and Pfeiffer)	*FGFR2* (*Fgfr2c*$^{C342Y/+}$)	Significantly reduced nasal passage volume (despite generally larger craniofacial complex), increased cross-sectional area of paraseptal cartilage						Despite reduced nasal volumes, Crouzon mice had no facial sutures fused with high frequency in this study. Unlike in Apert mice, facial bone tethering may be less likely the main driver of facial deformity in Crouzon mice

Holmes et al[23] (2018)	Crouzon (and Pfeiffer)	*FGFR2* (*Fgfr2c*$^{C342Y/+}$)	Shortened skull, nose, and maxilla; increased skull width; shortened anterior cranial base	FN	Failed attempt to reverse suture synostoses (frontonasal and coronal) with a pharmacologic inhibitor of FGFR signaling developed for achondroplasia (BMN 111)

No synostosis of sutures in the orbital, nasal, mandibular, or circumneatal regions was characterized by these studies, so these regions are not included in this table.
FM, frontomaxillary; FN, frontonasal; FP, frontopremaxillary; IP, interpremaxillary; IS, intersphenoidal; MxP, maxillopalatine; PrMx, premaxillary-maxillary; SO, spheno-occipital; ZM, zygomaticomaxillary; ZT, zygomaticotemporal.

and cranial base synchondroses, respectively. A later study cataloguing the craniofacial deformities of *Twist1*$^{+/-}$ mice, including facial widening and shortening, hypothesized that these abnormalities may be secondary to facial suture pathology but acknowledged that a thorough examination of facial sutures had yet to be performed in this mutant model.[50]

DISCUSSION

Virtually ubiquitous among patients, facial deformities in syndromic craniosynostosis are functionally and aesthetically impairing.[6] The possibility of severe complications is compounded by psychosocial consequences from disfigurement.[8,9,12,13] Improving management first necessitates achieving a robust understanding of how these deformities develop. The current leading cranial base theory has overshadowed the robust, multidisciplinary knowledge base supporting the pathologic role of facial suture synostosis.[15–19]

Research in mouse models provides captivating evidence that premature facial suture fusion, even without cranial base involvement, produces key facial deformities.[15–17,23] These findings support early work by Sarnat,[3] Björk,[52] Björk and Skieller,[53] and Enlow and Hunter[4] demonstrating that normal adult midfacial growth processes require precise postnatal osteogenesis at facial sutures. Exciting insights in nonsyndromic craniosynostosis highlight that discrete facial skeletal anomalies are attributable to defined facial suture synostosis patterns.[39,41] Finally, although Runyan et al[25] and Calandrelli et al[24] recently pioneered the investigation of facial region sutures in syndromic patients, their limitations and overall scarcity of related research underscore a significant gap in the literature. Without additional investigation, the possibility that facial synostosis is also a primary pathology driving syndromic facial deformity cannot be excluded.

Juxtaposing syndromic facial deformities with postnatal facial growth modalities further supports a putative role for facial synostosis. The CT studies by Forte et al[10] and Calandrelli et al[24] assiduously demonstrate that the facial bones of syndromic patients are not volumetrically deficient compared with those of normal controls. Rather, midfacial deformities are associated with 2 distinct findings: maxillary retrusion and dimensional anomalies.

Postnatal facial growth occurs through cranial base endochondral growth, appositional and resorptive growth at bone surfaces, and facial sutural growth.[3] Although premature cranial base ossification may inhibit full protrusion of the maxilla, it is unlikely to independently account for the dimensional abnormalities in individual facial bones characterized by Forte et al[10] and Calandrelli et al.[24] Instead, facial sutural growth is understood to exert a finer, nuanced effect on how adjacent viscerocranial bones expand in relation to each other.[1] Therefore, dimensional deviations may be more aptly hypothesized to be secondary to sutural pathology. The observation that facial bones of syndromic patients are dimensionally deformed and not volumetrically hypoplastic suggests that the underlying pathologies disrupt calibrated growth processes more so than those of active expansion. We hereby provide a framework to conceptualize how cranial base and facial suture pathology could synergistically drive facial deformity in syndromic craniosynostosis.

Refocusing clinical research on facial sutures is necessary to achieve a more complete understanding of syndromic facial deformity. The previously mentioned studies mark a tangible step in the right direction, but future research needs to address their limitations.[24,25]

From this comprehensive review, we identify the need for an in vivo imaging study longitudinally evaluating facial osteology across craniosynostosis syndromes. By integrating the longitudinal design of Runyan et al,[25] the volumetric cephalometry of Forte et al,[10] and the comprehensive coverage of viscerocranial sutures of Calandrelli et al.[24] such a study would enable a robust investigation of facial suture closure timing, dynamics, and relationship with facial deformity. Particular

attention should be paid to those sutures (frontomaxillary, frontozygomatic, zygomaticomaxillary, intermaxillary, and midpalatal) with prominent roles in postnatal midfacial growth.[3,4,52,53]

The study should rigorously evaluate each patient's degree of cranial base ossification versus facial suture synostosis over time. Simultaneously, it should characterize their facial skeletal phenotype, analyzing individual contributions from malpositioning (ie, retrusion), dimensional deformity, and perhaps even volumetric hypoplasia. In doing so, the study could correlate the presence (and degree) of various etiologic pathologies with the magnitude of consequent facial anomalies. By quantifying how cranial base and facial suture pathologies variably contribute to these anomalies, this study would also test our framework that these 2 etiologic factors drive distinct aspects of facial deformity.

The proposed design also mitigates key limitations of prior research. Ideally, preoperative and postoperative CTs should be tracked longitudinally from birth through the plateau of facial growth in adolescence.[1] Capturing this age range optimizes detection of premature suture synostoses and cranial base ossifications, while enabling progression monitoring. Although longitudinal tracking is practically limited by the need to minimize radiation, iterative CTs are often already obtained in patients with complex craniofacial malformations undergoing staged surgical corrections.[54,55]

Facial sutures should also be studied to improve surgical management. Current standard corrective procedures, such as Le Fort III and Monobloc advancements, involve mobilizing large bone flaps with nonnegligible morbidity and even mortality risk.[9,56,57] Even with distraction, these large manipulations commonly have suboptimal aesthetic and functional outcomes as they offer limited ability to correct granular, but significant deformities on the individual bone level.[10,58] Moreover, these techniques are not intended to correct sutural pathology. Optimal outcomes are perhaps not achieved because despite surgical advancement en bloc, adjacent facial bones may remain tethered and underdeveloped from unresolved suture disruption. Newer modifications, such as Le Fort II distraction with zygomatic repositioning for Apert patients, increasingly acknowledge these shortcomings and incorporate additional osteotomies to enable more meticulous reconstruction of midfacial concavity.[59] Although longitudinal cephalometric studies will be required, it is conceivable that distracting these osteotomies may help functionally restore aberrant sutural growth by redirecting osteogenesis at newly formed bone junctions.

Furthermore, osseous facial expansion persists through adolescence, while surgical intervention is often performed during early childhood.[9] If suture synostoses were at play, would early targeted release of affected sutures normalize some degree of subsequent growth? Evaluating sutures longitudinally in syndromic patients—even postoperatively—will be essential to answer this question. If CTs after facial advancement surgery continue to demonstrate suture synostosis while the patient's clinical outcome remains suboptimal, we may postulate that suture release could be beneficial by liberating the restricted growth vectors. Targeted facial suturectomy is already used in certain clinical contexts. Internasal suturectomy improves hypotelorism in severe trigonocephaly, while midpalatal and pterygomaxillary suturectomies are mainstay surgical treatments for adult transverse maxillary hypoplasia.[41,60] Beyond surgery, the idea of introducing pharmacologic FGFR inhibitors directly into affected sutures to normalize growth is exciting but presently nascent.[23,61]

Ultimately, facial suture biology and facial deformity in syndromic craniosynostosis are intriguing topics within craniofacial reconstructive surgery, teeming with unanswered questions. More so than ever, the intersection of the two is ripe for future research.

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