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FGFR Craniosynostosis Syndromes Overview

Synonym: *FGFR* Acrocephalosyndactyly

Tara Wenger, MD, PhD,¹ Danny Miller, MD, PhD,¹ and Kelly Evans, MD¹

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding the *FGFR* craniosynostosis syndromes and their management.

Goal 1

Describe the clinical characteristics of *FGFR* craniosynostosis syndromes.

Goal 2

Review the genetic causes of *FGFR* craniosynostosis syndromes.

Goal 3

Provide an evaluation strategy to identify the genetic cause of an *FGFR* craniosynostosis syndrome in a proband.

Goal 4

Inform risk assessment and surveillance of at-risk relatives for early detection and treatment of *FGFR* craniosynostosis syndromes.

Goal 5

Summarize current management recommendations for individuals with an *FGFR* craniosynostosis syndrome.

Author Affiliation: 1 Seattle Children's Hospital, Seattle, Washington; Email: tara.wenger@seattlechildrens.org; Email: danny.miller@seattlechildrens.org; Email: kelly.evans@seattlechildrens.org.

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1. Clinical Characteristics of *FGFR* Craniosynostosis Syndromes

Clinical Description

To date, more than 500 individuals with an *FGFR* craniosynostosis syndrome have been reported. The spectrum of severity ranges from severe prenatal multisuture craniosynostosis with feeding and airway issues to isolated unicoronal craniosynostosis. Included in this overview are the following *FGFR* craniosynostosis phenotypes:

- Apert syndrome
- Beare-Stevenson cutis gyrata syndrome
- Bent bone dysplasia
- Crouzon syndrome
- Crouzon syndrome with acanthosis nigricans
- Jackson-Weiss syndrome
- Muenke syndrome
- Pfeiffer syndrome
- Isolated coronal synostosis

Considerable phenotypic overlap notwithstanding, discriminating features can aid in the specific diagnosis (see Table 1). The following individual phenotypes are recognized.

Apert syndrome

- **Craniofacial.** Head shape is determined by the sutures involved and the timing of premature fusion; the majority of individuals have some degree of turribrachycephaly. Midface retrusion is moderate to severe, with a greater degree of vertical impaction of the midface than most individuals with Crouzon syndrome [Forte et al 2014]. Additional common features include: ocular anomalies (e.g., proptosis, strabismus, refractive error, anisometropia), cleft palate, dental anomalies (crowding, delayed eruption, crossbite, missing teeth), and hearing loss (80%) that is most often conductive.
- **Respiratory.** Multilevel airway obstruction is common, including choanal stenosis, tongue-based airway obstruction, and tracheal anomalies.
- **Extremities.** Findings include soft tissue and bony ("mitten glove") syndactyly with or without polydactyly of fingers and toes often involving fusion of the second, third, and fourth digits with variable inclusion of the first and fifth digits; synonychia (a single nail for the second, third, and fourth digits) more commonly involving the upper extremities; synostosis of the radius and humerus in some individuals; and occasional rhizomelia [Cohen & Kreiborg 1995, Wilkie et al 1995].
- **Neurologic.** Variable developmental delay and/or intellectual disability (50%) is possibly related to the timing of craniofacial surgery [Renier et al 1996]; ventriculomegaly is common, progressive hydrocephalus is less common (2%); structural brain malformations (e.g., Chiari I malformation, absent septum pellucidum, agenesis of the corpus callosum) have been reported.
- **Gastrointestinal anomalies.** Malrotation is the most common [Hibberd et al 2016]. Congenital diaphragmatic hernia has been reported in five infants [Witters et al 2000, Bulfamante et al 2011, Sobaih & AlAli 2015, Kosiński et al 2016, Kaur et al 2019]. Distal esophageal stenosis, pyloric stenosis, esophageal atresia, and ectopic anus have all been reported [Cohen & Kreiborg 1993, Pelz et al 1994, Zarate et al 2010, Hibberd et al 2016].
- **Integument.** Hyperhidrosis, acneiform lesions, and nail dystrophy have been reported [Cohen & Kreiborg 1993, Cohen & Kreiborg 1995, Bissacotti Steglich et al 2016].
- **Other**
 - Fused cervical and/or thoracic vertebrae (68%), usually C5-C6
 - Cardiac anomalies (10%) (e.g., ventricular septal defect, overriding aorta)

- Ovarian dysgerminoma (1 individual) [Rouzier et al 2008]. A single instance of low-grade papillary urothelial carcinoma was reported. It is unclear if these tumors are related to Apert syndrome.

Beare-Stevenson cutis gyrata syndrome

- **Craniofacial.** Multisuture craniosynostosis with cloverleaf skull is the most common skull configuration. Moderate-to-severe midface retrusion, proptosis, abnormal ears, cleft palate, conductive hearing loss, natal teeth, and relative prognathism are seen.
- **Respiratory.** Multilevel airway obstruction includes choanal stenosis, tongue-based airway obstruction, and tracheal anomalies, with survivors requiring endotracheal intubation with mechanical ventilation and/or tracheostomy.
- **Extremities.** Hands and feet are normally formed aside from cutis gyrata.
- **Neurologic.** Intellectual disability is present in all affected individuals who have survived (neonatal mortality is common). Hydrocephalus and Chiari I malformations are common.
- **Integument.** Widespread cutis gyrata and acanthosis nigricans are usually evident at birth; hirsutism, skin tags, prominent umbilicus with redundant tissue, and accessory nipples are also seen.
- **Other findings** include genitourinary anomalies (e.g., bifid scrotum, prominent labial raphe, rugated labia majora), pyloric stenosis, and anterior anus.

Bent bone dysplasia

- **Craniofacial.** Variable features include hypomineralization of the calvarium, coronal craniosynostosis, open metopic suture, hypertelorism, megalophthalmous, midface hypoplasia, low-set posteriorly rotated ears overfolded superior helix, hypoplastic ears, gingival hyperplasia, prenatal teeth, and micrognathia [Merrill et al 2012].
- **Respiratory.** Perinatal lethal skeletal dysplasia with bell-shaped thorax
- **Extremities.** Bent long bones, osteopenia, irregular periosteal surfaces (especially the phalanges), brachydactyly
- **Gastrointestinal.** Hepatosplenomegaly, extramedullary hematopoiesis
- **Integument.** Hirsutism.
- **Other.** Osteopenia, hypoplastic clavicles, narrow ischia, hypoplastic pubis, clitoromegaly

Crouzon syndrome

- **Craniofacial.** Craniosynostosis in most individuals. Head shape depends on the sutures involved and the timing of premature fusion, ranging from normal head shape to cloverleaf skull. Infants without craniosynostosis may have normal facial features at birth with craniofacial features developing over the first year or two of life including: significant proptosis, external strabismus, midface retrusion, convex nasal ridge, and relative prognathism. Facial features can be highly variable among affected family members. High arched palate is common; cleft palate is less common. Hearing loss occurs in 74% and is most often conductive.
- **Respiratory.** Variable from no airway issues to multilevel airway obstruction including choanal stenosis, tongue-based airway obstruction, and tracheal anomalies
- **Extremities.** Normal (although shortened phalanges compared to unaffected family members have been identified on x-ray) [Murdoch-Kinch & Ward 1997]
- **Neurologic.** Structural brain malformations are uncommon; Chiari I malformation, progressive hydrocephalus (30%) often with tonsillar herniation have been reported. Most individuals have normal intelligence, although there is a risk for developmental delays, especially in individuals with hydrocephalus and increased intracranial pressure. A study of 31 adults with Crouzon syndrome reported a lower level of education, lower chance of having a romantic partner, and fewer children. There were no differences in housing type, and affected individuals' estimation of their overall health was similar to healthy controls

with the exception of a higher use of anti-seizure medication. Depressed mood was more common in individuals with Crouzon syndrome, but overall positive attitude to life was similar to control individuals. There was significant variability among affected individuals [Fischer et al 2014].

- **Integument.** Linear skin rugations, deep creases, and redundant scalp skin (similar to those seen in Beare-Stevenson cutis gyrata syndrome) were reported in individuals with pathogenic variants c.Ser267Pro and c.Val274_Glu275delinsLeu [LeBlanc et al 2018].
- **Other.** Approximately 25% have vertebral fusion, most often C2-C3. Sacrococcygeal appendage has also been described [Lapunzina et al 2005].

Crouzon syndrome with acanthosis nigricans

- **Craniofacial.** Craniosynostosis with variable head shape depending on involved sutures. Significant proptosis, external strabismus, prognathism. Hearing loss is reported in 14%.
- **Respiratory.** Variable from no airway issues to multilevel airway obstruction including choanal stenosis, tongue-based airway obstruction, and tracheal anomalies
- **Extremities.** Normal (although shortened phalanges compared to unaffected family members have been identified on x-ray) [Murdoch-Kinch & Ward 1997]
- **Neurologic.** Intellect is typically normal, although there is a risk for developmental delay especially in children with increased intracranial pressure as a result of hydrocephalus.
- **Integument.** Acanthosis nigricans (pigmentary changes in the skin fold regions) can be present in the neonatal period or appear later.
- **Other.** Odontogenic tumors have been reported [Xu et al 2018].

Jackson-Weiss syndrome

- **Craniofacial.** Multisuture craniosynostosis with proptosis and prognathism; hearing loss (68%) is usually conductive.
- **Respiratory.** Variable from no airway issues to multilevel airway obstruction including choanal stenosis, tongue-based airway obstruction, and tracheal anomalies
- **Extremities.** Broad and medially deviated great toes, with 2/3 toe syndactyly, and normal hands; short first metatarsal, calcaneocuboid fusion, and abnormally formed tarsals; genu valgum
- **Neurologic.** Intellect is typically normal.

Muenke syndrome. Some individuals have no apparent features and are only identified after they have a child diagnosed with Muenke syndrome.

- **Craniofacial.** Variable features including uni- or bicoronal craniosynostosis; unicoronal synostosis, more often seen in males [Honnebier et al 2008]; in some individuals, absence of craniosynostosis and normal or macrocephalic head shape; mild-to-significant midface retrusion; hypertelorism; bilateral, symmetric, low- to mid-frequency sensorineural hearing loss (61%) [Honnebier et al 2008].
- **Extremities.** Variable. Carpal and tarsal fusions are diagnostic when present but are not always present. Brachydactyly, carpal bone malsegregation, or coned epiphyses may occur.
- **Neurologic.** Intelligence ranges from normal to mild intellectual disability; social difficulties and mild neuropsychiatric issues (e.g., attention-deficit/hyperactivity disorder) are more common compared to unaffected sibs. Seizures are reported in 20% of individuals.
- **Other.** Osteochondroma [Barbosa et al 2009]

Pfeiffer syndrome shares significant phenotypic overlap with Crouzon syndrome, and individuals with the same pathogenic variant have been diagnosed with either Pfeiffer or Crouzon syndrome, although some *FGFR* pathogenic variants have been reported only in individuals with Pfeiffer syndrome.

- **Craniofacial.** Multisuture craniosynostosis in most individuals. Head shape depends on the sutures involved and the timing of premature fusion, ranging from normal head shape to cloverleaf skull. Individuals without craniosynostosis have been described. Midface retrusion is moderate to severe, with a greater degree of vertical impaction of the midface compared to individuals with Crouzon syndrome [Forte et al 2014]. In individuals with severe craniosynostosis with shallow orbits, eyes are very prominent and there is a risk for subluxation of the globe. Hearing loss occurs in 92% and is most often conductive. Hearing loss may be associated with stenosis or atresia of the external auditory canal. Some individuals have cleft palate [Stoler et al 2009].
- **Respiratory.** Some individuals have multilevel airway obstruction, including choanal stenosis/atresia, laryngotracheal abnormalities including tracheal cartilaginous sleeve, and tongue-based airway obstruction.
- **Extremities.** Thumbs and great toes are broad and medially deviated, with a variable degree of brachydactyly. Synostosis of the radius and humerus occurs in some individuals particularly those with *FGFR2* pathogenic variant p.Trp290Cys. Ankylosis of the knees has been reported. In one family, involvement of the feet was the only clinical feature [Rossi et al 2003].
- **Neurologic.** Intelligence ranges from normal to severe intellectual disability. Seizures and an increased risk for early death are reported. Early surgery to prevent cephalocranial disproportion and intervention to manage sleep apnea may promote improved cognitive outcomes in children with severe presentations [Wenger et al 2019]. Approximately 28% of children require surgical intervention for hydrocephalus [Cinalli et al 1998]. Approximately 50% of individuals with cloverleaf skull have Chiari I malformation [Cinalli et al 1995].
- **Other.** Sacroccocygeal eversion/appendage has been described [Oliveira et al 2006, Lai et al 2008]. Prune belly has been reported in two infants [Bracero et al 1988, Peña-Padilla et al 2019].

Isolated coronal synostosis

- Intellect. Normal
- Craniofacial. Unilateral or bilateral coronal synostosis, asymmetric brachycephaly and/or orbital hypertelorism
- Extremities. Normal

Table 1. Distinguishing Characteristics of *FGFR* Craniosynostosis Syndromes

Phenotype	Craniosynostosis	Additional Craniofacial/ Airway Features	Hands/Feet	Neurologic	Other
Apert syndrome	Multisuture craniosynostosis, typically incl coronal sutures	<ul style="list-style-type: none"> • Midface retrusion, proptosis • Cleft palate • CHL • Dental anomalies • Multilevel airway obstruction 	<ul style="list-style-type: none"> • Soft tissue & bony syndactyly w/or w/o polydactyly of fingers & toes • Synonychia 	<ul style="list-style-type: none"> • ID (~50%) • Stable ventriculomegaly (>50%) • Chiari I, absent septum pellucidum, agenesis corpus callosum 	<ul style="list-style-type: none"> • Vertebral fusions (often C5-C6) • Hyperhidrosis • Acne • Nail dystrophy

Table 1. continued from previous page.

Phenotype	Craniosynostosis	Additional Craniofacial/Airway Features	Hands/Feet	Neurologic	Other
Beare-Stevenson cutis gyrata syndrome	Multisuture craniosynostosis, cloverleaf skull in most individuals	<ul style="list-style-type: none"> Severe midface retrusion w/ proptosis Cleft palate CHL Natal teeth Multilevel airway obstruction 	Normal	<ul style="list-style-type: none"> ID (100%) Hydrocephalus Chiari I 	<ul style="list-style-type: none"> High rate of neonatal death Cutis gyrata Acanthosis nigricans Hirsutism
Bent bone dysplasia	Coronal	<ul style="list-style-type: none"> Open metopic suture Hypertelorism Midface hypoplasia Prenatal teeth Low-set ears 	<ul style="list-style-type: none"> Brachydactyly Bony nodules on phalanges & metacarpals 	Lethal, no data	<ul style="list-style-type: none"> Hepatosplenomegaly Clitoromegaly Hirsutism
Crouzon syndrome	Variable multisuture craniosynostosis; may occur later in childhood	<ul style="list-style-type: none"> Variable midface retrusion & proptosis ↑ w/ age. CHL & SNHL ± airway obstruction 	Typically normal	<ul style="list-style-type: none"> Hydrocephalus Chiari I ID uncommon 	Vertebral fusions in 25% (often C2-C3)
Crouzon with acanthosis nigricans	Variable multisuture craniosynostosis; may occur later in childhood	<ul style="list-style-type: none"> Variable midface retrusion & proptosis ↑ w/ age. CHL & SNHL ± airway obstruction 	Normal	<ul style="list-style-type: none"> Hydrocephalus Chiari I ID uncommon 	Acanthosis nigricans
Jackson-Weiss syndrome	Multisuture craniosynostosis	<ul style="list-style-type: none"> Proptosis CHL ± multilevel airway obstruction 	<ul style="list-style-type: none"> Broad medially deviated great toes, 2/3 syndactyly, tarsal &/or metatarsal fusion Normal hands 	Most w/normal intelligence	Genu valgum
Muenke syndrome	Uni- or bicoronal craniosynostosis (85%)	<ul style="list-style-type: none"> Variable midface retrusion & proptosis SNHL 	<ul style="list-style-type: none"> Brachydactyly Carpal & tarsal fusions 	<ul style="list-style-type: none"> DD (66%) ID (36%) ADHD (24%) Seizures (20%) 	

Table 1. continued from previous page.

Phenotype	Craniosynostosis	Additional Craniofacial/Airway Features	Hands/Feet	Neurologic	Other
Pfeiffer syndrome	Most w/ multisuture craniosynostosis, some w/ cloverleaf skull	<ul style="list-style-type: none"> • Most w/ moderate to severe midface retrusion & proptosis • CHL • ± multilevel airway obstruction 	<ul style="list-style-type: none"> • Broad medially deviated thumbs & great toes • ± brachydactyly 	<ul style="list-style-type: none"> • Hydrocephalus • Chiari I • ID 1 	<ul style="list-style-type: none"> • ± fusions at elbows and knees • ± sacral appendage
Isolated coronal synostosis	Uni- or bicoronal craniosynostosis	<ul style="list-style-type: none"> • Proptosis if bicoronal craniosynostosis • Variable midface retrusion 	Normal	See footnote 2.	

ADHD = attention-deficit/hyperactivity disorder; CHL = conductive hearing loss; DD = developmental delay; ID = intellectual disability; SNHL = sensorineural hearing loss

1. Intellectual disability is common in those with severe craniosynostosis but may be lessened with aggressive medical and surgical management of cephalocranial disproportion and sleep apnea.

2. Infants with *FGFR2* isolated coronal synostosis may develop features of Crouzon or Muenke syndromes over time.

Clinical Complications

Common complications that affect medical management for *FGFR* craniosynostosis syndromes are described in this section. Unless otherwise indicated, the following general descriptions do not include Muenke syndrome or isolated coronal synostosis.

Craniosynostosis. The majority of individuals with an *FGFR* craniosynostosis syndrome have congenital craniosynostosis. However, craniosynostosis can also develop later in infancy or childhood, and individuals with congenital craniosynostosis can prematurely fuse additional sutures over time. Individuals with Muenke syndrome are more likely to have premature fusion of coronal sutures only, while other *FGFR* craniosynostosis syndromes (e.g., Apert, Crouzon, Pfeiffer) are associated with progressive postnatal premature fusion of sutures.

Unicoronal craniosynostosis results in asymmetric forehead with nasal twist and harlequin eye deformity. Bicoronal craniosynostosis results in turribrachycephaly.

Multisuture craniosynostosis results in a variable head shape determined by the involved sutures, presence of hydrocephalus, and timing of premature fusion. The shape of the skull results from the pressure of the developing brain expanding outwards into the space allowed by the skull. There is typically expansion perpendicular to the fused suture. When multiple sutures are fused, expansion occurs into the portion of the skull with least resistance, resulting in predictable head shapes. Prenatal pansynostosis results in a cloverleaf (*Kleeblatschadel*) head shape. Pansynostosis that occurs later in infancy or childhood does not result in a cloverleaf head shape, and may only be identified on head CT with an arrest in head circumference growth. Affected individuals may or may not have microcephaly.

Feeding issues can be multifactorial, and can be caused by any of the following:

- Palatal anomalies affecting the quality of suck (e.g., high arched palate, narrow palate, cleft palate)
- Respiratory difficulties due to airway obstruction (e.g., choanal stenosis, choanal atresia, tracheomalacia, laryngomalacia). Infants with choanal stenosis or atresia attempt to latch but abruptly unlatch to breathe

through their mouth. The degree of narrowing of the bony passage correlates with the amount of time an infant can attempt to suck before unlatching.

- Ascending and/or descending aspiration
- Coordination difficulties with sucking, swallowing, and breathing, which may be seen without other signs of neurologic dysfunction
- Severe neurologic dysfunction (e.g., severe hydrocephalus, symptomatic Chiari I malformation)
- Gastrointestinal issues (e.g., pyloric stenosis, malrotation, volvulus)

Multilevel airway obstruction. Most individuals have some degree of airway obstruction, though contributing factors can vary with age:

- Narrowed nasal passages as a result of bony atresia or stenosis, including choanal atresia or stenosis. For infants with choanal stenosis respiratory difficulty can increase over time as the bony passage remains relatively stable but the lung tidal volumes increase with growth. Infants with choanal stenosis may gradually require more time to finish a smaller volume. Nasal flaring, retractions, and repeated unlatching during a feeding with mouth breathing can be seen.
- Tongue-based airway obstruction, which may be exacerbated in infants with cleft palate after palate repair
- Tracheal anomalies including fused rings and tracheal cartilaginous sleeves. Tracheal cartilaginous sleeves are often asymptomatic but harbor a significant risk of sudden death caused by obstruction of the airway with mucous during illness. Tracheal cartilaginous sleeves can be identified during operative airway evaluation, as recommended for all children with a multisuture craniosynostosis syndrome [Pickrell et al 2017, Wenger et al 2017].
- Airway inflammation as a result of chronic aspiration

Sleep apnea. Obstructive sleep apnea (OSA), caused by multilevel airway obstruction, may develop or worsen during childhood or adulthood. The majority of individuals with *FGFR* craniosynostosis syndromes have midface retrusion, which can contribute to obstructive sleep apnea. This can be challenging to treat, as continuous-positive-airway-pressure masks place pressure on the maxillae and can worsen midface retrusion with consistent wear during childhood, which can produce more airway resistance and potentially worsen OSA [Driessen et al 2013].

Central sleep apnea is more common in children with Chiari I malformation and/or significant hydrocephalus. Children with Pfeiffer syndrome as a result of *FGFR2* pathogenic variant p.Trp290Cys appear to be particularly susceptible to central sleep apnea, and 100% of reported surviving individuals have required mechanical ventilation during sleep for at least some period of time [Wenger et al 2019].

Ocular abnormalities. Coronal craniosynostosis and underdevelopment of the maxillary arches results in decreased depth of the bony orbit and proptosis. Some individuals with particularly shallow orbits have globe subluxation (i.e., eyelids retract behind the globe). Individuals with proptosis often have difficulty keeping their eyes closed fully while asleep leading to exposure keratopathy and corneal scarring.

Individuals with mild involvement of the bony orbit may have downslanted palpebral fissures. Other ophthalmologic abnormalities include strabismus, refractive error, anisometropia, iris hypoplasia, and posterior embryotoxon [McCann et al 2005].

In individuals with increased intracranial pressure – particularly if there is not prompt and aggressive intervention – papilledema can occur, leading to optic atrophy and loss of vision.

Hearing loss. Conductive hearing loss is more common than sensorineural for all *FGFR* craniosynostosis syndromes except Muenke syndrome.

Dental anomalies. Tooth agenesis, enamel opacities, and abnormal patterns of tooth eruption are common. Dental maturation is more significantly delayed in individuals with Apert than Crouzon syndrome [Reitsma et al

2014]. There is often dental crowding, especially in the maxillary arch. Most children develop malocclusion as a result of progressive maxillary retrusion and/or abnormalities in mandibular growth [Kolar et al 2017].

Limb anomalies. Synostosis of the radius and humerus occurs in some individuals, most commonly in those with Apert syndrome, occasionally in those with Pfeiffer syndrome, especially in those with *FGFR2* pathogenic variant p.Trp290Cys. Upper-arm mobility may also be limited by glenohumeral dysplasia, leading to progressive decrease in forward flexion and abduction of the upper arm, limiting the ability to perform overhead tasks. Some individuals have an increased susceptibility to fractures, including femoral fractures [Author, unpublished data]. Broad, medially deviated thumbs and great toes are characteristic of Pfeiffer syndrome. Mildly broad thumbs have been reported in individuals with other *FGFR* craniosynostosis syndromes. Preaxial and/or postaxial polydactyly are rare [Mantilla-Capacho et al 2005].

Vertebral anomalies. Vertebral fusions are more common in individuals with Apert syndrome than Crouzon syndrome. Approximately half of individuals with vertebral fusions have multiple fusions. This can result in scoliosis and/or instability [Shotelersuk et al 2002, Lin et al 2019]. Cervical spine instability has been reported. Some children have been reported to have atlanto-axial subluxation and C1 spina bifida occulta [Breik et al 2016].

Neurologic. Hydrocephalus is a prominent feature of Crouzon and Pfeiffer syndromes and may occur at any time. Many children with Crouzon and Pfeiffer syndromes who have multisuture craniosynostosis require a surgical treatment for obstructive hydrocephalus (e.g., ventriculoperitoneal shunt, endoscopic third ventriculostomy) within the first two to three years of life, and some require intervention early in infancy. The foramen magnum develops differently and intra-occipital synchondroses may fuse early in each of the *FGFR* craniosynostosis syndromes, which may contribute to hydrocephalus and abnormal head shape [Rijken et al 2015, Coll et al 2018]. Stable ventriculomegaly is seen in more than half of children with Apert syndrome, and these children are much less likely to require surgical interventions for hydrocephalus.

Structural brain anomalies are more common in individuals with Apert syndrome, including abnormalities of the corpus callosum, absent septum pellucidum, posterior fossa arachnoid cyst, and limbic malformations. Chiari I malformations and/or low-lying cerebellar tonsils can be seen, and 73% of those with Crouzon syndrome have been reported to have chronic tonsillar herniation. This is in stark contrast to Apert syndrome, where only 2% have chronic tonsillar herniation.

Neurodevelopment ranges from normal to severe intellectual disability. Most children with significant impairments have had cloverleaf skull, structural brain anomalies, and/or significant hydrocephalus. For children with multisuture craniosynostosis, early and aggressive surgical intervention to address increased intracranial pressure may prevent intellectual disability [Wenger et al 2019]. Neurobehavioral and developmental challenges may also be as a result of hearing impairment, vision impairment, physical limitations (e.g., limb anomalies), and sleep apnea.

Cardiovascular. Structural cardiac defects occur in approximately 10% of individuals with Apert syndrome but are uncommon in individuals with Crouzon and Pfeiffer syndromes. Complex congenital heart disease is associated with an increased risk of morbidity and mortality because of the cardiac lesion as well as with other procedures (e.g., positive pressure ventilation via tracheostomy can contribute to poor outcomes in children with single-ventricle physiology). Cardiac defects that result in atrial shunts can increase the risk of embolic stroke during craniosynostosis surgery. Children with severe, untreated obstructive sleep apnea can develop right ventricular hypertrophy and pulmonary hypertension.

Other

- **Gastrointestinal.** Structural malformations include malrotation, pyloric stenosis, and esophageal atresia.
- **Genitourinary.** Hydronephrosis and cryptorchidism have been reported.

Prognosis. Multigenerational families with Crouzon and Apert syndromes have been reported. Many adults with Crouzon syndrome and some with Apert syndrome are fully independent, though some individuals have physical or cognitive limitations that require assistance.

Differential Diagnosis

Craniosynostosis can be primary or secondary. In primary craniosynostosis, abnormal biology of the suture causes premature suture closure, as in *FGFR* craniosynostosis syndromes. Primary craniosynostosis can be isolated or part of a syndrome.

In secondary craniosynostosis, the suture biology is normal, but abnormal external forces result in premature suture closure.

Isolated Primary Craniosynostosis

Single-suture craniosynostosis results in recognizable head shapes: metopic (trigonocephaly), sagittal (scaphocephaly), lambdoid (posterior asymmetric flattening with vertical displacement of one ear and tilt of skull base), unicoronal (asymmetric forehead with nasal twist and harlequin eye deformity), and bicoronal (turribrachycephaly).

Among 204 individuals with apparently nonsyndromic and nonfamilial single-suture craniosynostosis, the likelihood of finding an underlying genetic difference varied by suture involvement [Wilkie et al 2010, Mathijssen 2015].

- **Isolated unicoronal craniosynostosis.** Among individuals with apparently nonsyndromic unicoronal craniosynostosis the prevalence of any syndrome was 17%; Muenke syndrome was identified in 10%.
- **Isolated bicoronal craniosynostosis.** Among individuals with apparently isolated bicoronal craniosynostosis, Muenke syndrome was diagnosed in 38%; no other syndromes were identified.

Note: (1) Those with apparently isolated synostosis of the lambdoid, sagittal, or metopic sutures had no pathogenic variants identified [Wilkie et al 2010, Mathijssen 2015]. (2) A study in individuals with either syndromic or nonsyndromic metopic craniosynostosis found no pathogenic variants in *FGFR1*, *CER1*, or *CDON*, suggesting that analysis of these genes is not warranted in persons with metopic craniosynostosis [Jehee et al 2006].

Syndromic Primary Craniosynostosis

Craniosynostosis is a finding in more than 150 genetic disorders. Additional syndromes that should be considered are included in Table 2.

Table 2. Syndromes of Interest in the Differential Diagnosis of *FGFR* Craniosynostosis Syndromes

Gene(s)	Disorder	MOI	Clinical Features of Differential Disorder		
			Craniosynostosis	Facial features	Hand & foot findings
CD96	Opitz trigonocephaly syndrome (C syndrome) (OMIM 211750)	AD	Trigonocephaly	Micrognathia, epicanthal folds, upslanted palpebral fissures, strabismus, anteverted nares, broad nasal bridge, short nose, macrostomia	Postaxial polydactyly, clinodactyly, ulnar deviation of fingers, terminal transverse limb reduction, metacarpal hypoplasia, syndactyly

Table 2. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Differential Disorder		
			Craniosynostosis	Facial features	Hand & foot findings
<i>EFNB1</i>	Craniofrontonasal syndrome (OMIM 304110)	XL	Coronal	Asymmetric frontal bossing, low posterior hairline, widow's peak, hypertelorism, broad bifid nose, ± cleft lip & palate	Hands/feet: splitting nails, fingers & toes deviated distally or hypoplastic
<i>FLNA</i>	X-linked otopalatodigital spectrum disorders	XL	Variable	Variable	Variable, hypoplasia of 1st digit of hands & feet
<i>GLI3</i>	Greig cephalopolysyndactyly syndrome	AD	Macrocephaly	Frontal bossing, hypertelorism, wide nasal bridge	Polydactyly of the hands (often postaxial), & feet w/ syndactyly of toes 1-3 & often a duplicated hallux
<i>IHH</i> ¹	Philadelphia-type craniosynostosis ²	AD	Sagittal	Prominent forehead	Hands/feet: cutaneous syndactyly
<i>MSX2</i>	Boston-type craniosynostosis (OMIM 604757)	AD	Coronal; cloverleaf skull	Fronto-orbital recession or frontal bossing	Feet: short 1st metatarsals
<i>POR</i>	Antley-Bixler syndrome (See Cytochrome P450 Oxidoreductase Deficiency .)	AR	Brachycephaly or turriccephaly	Midface retrusion	Hands: arachnodactyly, clinodactyly, camptodactyly, metacarpal synostoses, wrist deviation Feet: rocker-bottom, metatarsal synostoses, talipes
<i>RAB23</i>	Carpenter syndrome (OMIM 201000)	AR	Variable sagittal, lambdoid & coronal; acrocephaly	Midface retrusion, flat nasal bridge, epicanthal folds, corneal opacity	Hands: brachydactyly, syndactyly, aplasia/hypoplasia of middle phalanges Feet: preaxial polydactyly
<i>RECQL4</i>	Baller-Gerold syndrome	AR	Coronal or lambdoid; brachycephaly	Proptosis, prominent forehead	Hands: radial ray defect (thumb aplasia/hypoplasia, radius aplasia/hypoplasia)
<i>SKI</i>	Shprintzen-Goldberg syndrome	AD	Coronal, sagittal, or lambdoid	Tall or prominent forehead, proptosis, hypertelorism, downslanted palpebral fissures, malar flattening	Hands: arachnodactyly; camptodactyly Feet: malposition, pes planus
<i>SOX9</i>	Campomelic dysplasia	AD	Not observed	Micrognathia, midface hypoplasia, macrocephaly, Pierre Robin sequence	Shortening of phalanges in hands & feet, talipes equinovarus
<i>TGFBR1</i> <i>TGFBR2</i>	Loeys-Dietz Syndrome	AD	Sagittal; dolichocephaly	Hypertelorism, bifid uvula ± cleft palate	Pes planus
<i>TWIST1</i>	Saethre-Chotzen syndrome	AD	Coronal (uni- or bilateral)	Low frontal hairline, ptosis, strabismus, facial asymmetry	Hands: ± 2/3 syndactyly

AD = autosomal dominant; AR = autosomal recessive; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. Klopocki et al [2011]

2. Robin et al [1996]

See [Craniosynostosis: OMIM Phenotypic Series](#) to view genes associated with this phenotype in OMIM.

Secondary craniosynostosis. In children with deficient brain growth, all cranial sutures fuse prematurely and the head is symmetric and microcephalic. Abnormal head positioning in utero or in infancy may also produce an abnormal head shape (plagiocephaly); the abnormality often resolves with appropriate head positioning but occasionally results in craniosynostosis [Hunt & Puczynski 1996, Kane et al 1996].

2. Causes of *FGFR* Craniosynostosis

Three genes, *FGFR1*, *FGFR2*, and *FGFR3*, are associated with *FGFR* craniosynostosis syndromes (Table 3).

Table 3. Molecular Genetics of Craniosynostosis Syndromes

Phenotype	Gene	Proportion of Affected Individuals w/a Pathogenic Variant Detectable in Gene	MOI	Comment
Apert syndrome	<i>FGFR2</i>	100%	AD	<i>FGFR2</i> pathogenic variants p.Ser252Trp & p.Pro253Arg are the most common cause of Apert syndrome. ¹ Intragenic deletions/duplications reported in 3 individuals ²
Beare-Stevenson cutis gyrata syndrome	<i>FGFR2</i>	100%	AD	Intragenic 63-bp deletion reported in 1 individual ³
Bent bone dysplasia	<i>FGFR2</i>	100%	AD	The causative <i>FGFR2</i> pathogenic variants in Bent bone dysplasia have been identified in the transmembrane domain only. ⁴
Crouzon syndrome	<i>FGFR2</i>	100%	AD	
Crouzon syndrome w/acanthosis nigricans	<i>FGFR3</i>	100%	AD	The causative <i>FGFR3</i> pathogenic variant in Crouzon syndrome w/acanthosis nigricans is p.Ala391Glu. ⁵
Jackson-Weiss syndrome	<i>FGFR2</i>	100%	AD	
Muenke syndrome	<i>FGFR3</i>	100%	AD	The causative <i>FGFR3</i> pathogenic variant in Muenke syndrome is p.Pro250Arg. ⁶
Pfeiffer syndrome	<i>FGFR1</i>	<5% ⁷	AD	
	<i>FGFR2</i>	>95%	AD	
	<i>FGFR3</i>	1 individual	AD	<i>FGFR3</i> pathogenic variant p.Ala391Glu reported in 1 person w/Pfeiffer syndrome ⁸
Isolated coronal synostosis	<i>FGFR2</i>	Rare ⁹	AD	
	<i>FGFR3</i>	<100% ⁹	AD	

1. Bochukova et al [2009]

2. Oldridge et al [1999], Bochukova et al [2009], Fenwick et al [2011]

3. Slavotinek et al [2009]

4. Merrill et al [2012]

5. Mulliken et al [1999]

6. Muenke et al [1997]

7. *FGFR1* Pfeiffer syndrome may be underdiagnosed because of variable severity, some individuals do not have craniofacial manifestations [Flöttmann et al 2015].

8. Rymer et al [2019]

9. It is unclear whether individuals reported to have *FGFR2* or *FGFR3* isolated coronal craniosynostosis later developed other *FGFR* phenotypes, as features of Crouzon and Muenke syndromes are progressive and difficult to appreciate in infancy.

3. Evaluation Strategies to Identify the Genetic Cause of an *FGFR* Craniosynostosis Syndrome in a Proband

An *FGFR* craniosynostosis syndrome should be suspected in fetuses and individuals presenting with classic or suggestive findings of uni- or bicoronal craniosynostosis or cloverleaf skull, characteristic facial features, and/or variable hand and foot findings (see Table 1). Note that these features can vary from severe and life threatening to extremely mild, and may not be apparent in an affected neonate. Features typically become more prominent with age.

Establishing a specific genetic cause of an *FGFR* craniosynostosis syndrome:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Is based on clinical and radiologic findings and the identification of a pathogenic variant in *FGFR1*, *FGFR2*, or *FGFR3*, and involves medical history, physical examination, imaging, family history, and genetic testing.

Note: As no formal clinical diagnostic criteria exist, specific diagnosis should be confirmed by genetic testing.

Medical History

An *FGFR* craniosynostosis syndrome should be suspected in a fetus with prenatal ultrasound findings of craniosynostosis involving the coronal sutures, especially cloverleaf skull, polysyndactyly, midface retrusion, and growth restriction. Bent bone dysplasia should be suspected in a fetus with features of a skeletal dysplasia including hypoplastic thorax with short ribs, short limbs, curved femurs, or skull deformity.

Physical Examination

A physical examination should include standard growth parameters (height, weight, head circumference) and address the following key issues:

- Abnormal head shape to evaluate for craniosynostosis as well as bulging fontanelle, which could suggest increased intracranial pressure
- Orbital protection and particular attention to whether the lids fully cover the eyes during sleep
- Nasal flaring, retractions or other signs of obstructive breathing, or inability to pass a nasogastric tube or suction catheter, suggestive of choanal stenosis/atresia
- Careful examination of hands and feet for polysyndactyly or thumb anomalies
- Range of motion of elbows and knees to evaluate for radioulnar synostosis and/or joint contractures
- Genitourinary exam for sacral appendage or other anomalies

Family History

A three-generation family history should be taken, with attention to relatives with clinical and radiographic manifestations of an *FGFR* craniosynostosis syndrome (e.g., specific questions about individuals with abnormal head shapes, prominent eyes, midface retrusion, skeletal dysplasia, and/or other structural birth defects. Relevant findings from direct examination or review of medical records (including results of molecular genetic testing) must be documented.

Molecular Genetic Testing

Approaches include **gene-targeted testing** (targeted analysis, single-gene testing, multigene panel) or **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Options for testing include the following.

Targeted analysis or single-gene testing can be considered in a proband with clinical features characteristic of a specific *FGFR* craniosynostosis syndrome (see Table 1).

- **Apert syndrome.** Targeted analysis of *FGFR2* pathogenic variants p.Ser252Trp and p.Pro253Arg
- **Beare-Stevenson cutis gyrate syndrome.** Targeted analysis of *FGFR2* pathogenic variants p.Ser372Cys and p.Tyr394Cys
- **Bent bone dysplasia.** Targeted analysis of *FGFR2* pathogenic variants p.Met391Arg and p.Tyr381Asp
- **Crouzon syndrome with acanthosis nigricans.** Targeted analysis of *FGFR3* pathogenic variant p.Ala391Glu
- **Jackson-Weiss syndrome.** Sequence analysis of *FGFR2* to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants can be performed first; typically, exon or whole-gene deletions/duplications are not detected. If no pathogenic variant is found, perform gene-targeted *FGFR2* deletion/duplication analysis to detect intragenic deletions or duplications.
- **Muenke syndrome.** Targeted analysis of *FGFR3* pathogenic variant p.Pro250Arg. Sequence analysis of *TCF12* should be considered next if no pathogenic variant is found (see Table 2).
- **Pfeiffer syndrome.** Sequence analysis of *FGFR2* to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants can be performed first; typically, exon or whole-gene deletions/duplications are not detected. If no pathogenic variant is found, perform gene-targeted *FGFR2* deletion/duplication analysis to detect intragenic deletions or duplications.

A **craniosynostosis multigene panel** that includes *FGFR1*, *FGFR2*, *FGFR3*, *TCF12*, *TWIST1*, and other genes of interest (see Table 2 and Table 3) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For these disorders a multigene panel that also includes deletion/duplication analysis is recommended (see Table 3).

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Comprehensive genomic testing (which does not require the clinician to determine which gene[s] are likely involved) can be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

4. Genetic Risk Assessment

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic

status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

The *FGFR* craniosynostosis syndromes are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- An individual with an *FGFR* craniosynostosis syndrome may have an affected parent or may have the disorder as the result of a *de novo* pathogenic variant.
 - With a milder phenotype – as can be seen in [Muenke syndrome](#), Crouzon syndrome, Pfeiffer syndrome, and Jackson-Weiss syndrome – inheritance of the pathogenic variant from an affected parent is common; in the most severe forms (e.g., bent bone dysplasia), *de novo* pathogenic variants are common.
 - *FGFR3* isolated coronal synostosis is usually inherited from a heterozygous parent who may or may not be affected.
- Molecular genetic testing and clinical and radiographic evaluations are recommended for the parents of a proband with an apparent *de novo* pathogenic variant
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.
- The family history of some individuals diagnosed with an *FGFR* craniosynostosis syndrome may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing and clinical and radiographic evaluations have been performed on the parents of the proband.
- If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic and germline mosaicism for the variant and may be asymptomatic or mildly/minimally affected. To date, Crouzon syndrome is the only *FGFR* craniosynostosis syndrome in which parental mosaicism has been reported.
- Note: Advanced paternal age has been shown clinically to be associated with *de novo* pathogenic variants for Crouzon syndrome, Apert syndrome, Pfeiffer syndrome [Glaser et al 2000], Beare-Stevenson cutis gyrata syndrome, and Muenke syndrome [Rannan-Eliya et al 2004]. Paternal age effect in *de novo* mutation has been conclusively demonstrated at the molecular level in Apert syndrome [Moloney et al 1996, Yoon et al 2009]. It has been proposed that *FGFR* pathogenic variants are paradoxically enriched in the male germline because they confer a selective advantage to the spermatogonial cells in which they arise [Goriely et al 2003, Choi et al 2008, Bochukova et al 2009, Yoon et al 2009].

Sibs of a proband. The risk to sibs of the proband depends on the genetic status of the proband's parents:

- If a parent is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
 - The *FGFR* craniosynostosis categorical phenotype is usually consistent within family members heterozygous for the same pathogenic variant, though the severity and specific manifestations can vary widely among affected individuals. For example, if the proband has the clinical findings of Pfeiffer syndrome, heterozygous sibs of the proband will likely have clinical findings that are also consistent with Pfeiffer syndrome rather than Crouzon, Jackson-Weiss, or Apert syndrome. Nonetheless, rare examples of varied phenotype among affected individuals in a given family have been reported: Moko & Blandin de Chalain [2001], Aravidis et al [2014], and Bessenyei et al [2014]

describe families in which some family members had findings suggestive of Pfeiffer syndrome, whereas others had findings suggestive of Jackson-Weiss or Crouzon syndromes.

- Significant differences in clinical severity of a given type of *FGFR* craniosynostosis syndrome may be observed in heterozygous sibs. For example, the sutures that are fused at birth and degree of respiratory support required may vary significantly in families with Crouzon syndrome. In families with Muenke syndrome, there is decreased penetrance of craniosynostosis and variability in hearing loss.
- If the *FGFR* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. Parental germline and somatic mosaicism in Crouzon syndrome has been reported [Goriely et al 2010].
- If the parents have not been tested for the pathogenic variant identified in the proband but are clinically unaffected, sibs are still presumed to be at increased risk for an *FGFR* craniosynostosis syndrome because of the possibility of reduced penetrance/variable expressivity in a heterozygous parent or parental germline mosaicism.
 - This risk appears to be low for Apert, Beare-Stevenson cutis gyrata, bent bone dysplasia, and Pfeiffer syndromes.
 - For Crouzon and Muenke syndromes, variable expressivity between family members necessitates careful clinical evaluation of apparently unaffected relatives as affected parents with mild manifestations (e.g., mild hearing loss, prominent eyes) may be unaware that they have features of the condition.

Offspring of a proband. Each child of an individual with an *FGFR* craniosynostosis syndrome has a 50% chance of inheriting the *FGFR* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *FGFR* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies. Once the *FGFR* pathogenic variant has been identified in an affected family member, molecular genetic prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

- The finding of an *FGFR* pathogenic variant cannot be used to predict the occurrence or severity of clinical manifestations for most *FGFR* phenotypes.
- The long-term prognosis of individuals with syndromes previously associated with poor outcomes is difficult to predict as advances in surgical management have dramatically changed expected outcomes from those suggested by historical data in the literature. For example, Wenger et al [2019] reported that all individuals with *FGFR2* p.W290C previously described in the literature had severe intellectual disability and/or early death but that three affected individuals who underwent aggressive surgical techniques designed to manage cephalocranial disproportion all had roughly normal neurocognitive development later in childhood.

Low-risk pregnancies. In a pregnancy not previously identified to be at risk for craniosynostosis in which an abnormal head shape is detected on prenatal ultrasound examination, prenatal testing is more difficult.

- **Molecular genetic testing.** While testing for pathogenic variants in *FGFR1*, *FGFR2*, or *FGFR3* is possible, the yield is likely to be low. Furthermore, identification of a pathogenic variant in one of these genes would not clarify the prognosis, which is determined by clinical findings (e.g., the prognosis for cloverleaf skull is generally poor regardless of the molecular defect or nature of hand and foot findings).
- **Prenatal imaging.** Prenatal testing of various craniosynostosis syndromes may be possible if physical findings including abnormal biparietal diameter and ventriculomegaly are apparent on prenatal imaging. Three-dimensional ultrasound examination, three-dimensional CT scan, and MRI have proven useful in some cases to further delineate suspicious ultrasound findings and assess for underlying brain abnormalities. Prenatal MRI is often used to accurately diagnose suspected craniosynostosis syndromes such as Pfeiffer or Apert syndromes. Findings detectable by MRI may include agenesis of the corpus callosum, hydrocephalus causing increased biparietal diameter, or cloverleaf skull [Tonni et al 2011, Ketwaroo et al 2015, Helfer et al 2016].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Born a Hero**
www.bornahero.org
- **American Cleft Palate-Craniofacial Association**
Phone: 919-933-9044
www.acpa-cpf.org
- **Children's Craniofacial Association**
Phone: 800-535-3643

Email: contactCCA@ccakids.com
www.ccakids.org

- **Face Equality International**
 United Kingdom
faceequalityinternational.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
Phone: 800-352-9424
 Craniosynostosis

5. Management of Individuals with an *FGFR* Craniosynostosis Syndrome

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with an *FGFR* craniosynostosis syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended. Note: For recommended evaluations following initial diagnosis of Muenke syndrome, see [Muenke Syndrome](#).

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *FGFR* Craniosynostosis Syndromes

System/Concern	Evaluation	Comment
Craniofacial	Physical exam to identify cleft palate, ear anomalies, face shape, fontanelles, suture ridging, head shape, & skull base symmetry	Assessing severity of maxillary hypoplasia is important to determine risk for airway compromise.
Eyes	Consultation w/pediatric ophthalmologist	Incl assessment of eye surfaces, eye alignment, & optic nerves.
Ears	Ear-specific hearing diagnostic eval	
Respiratory	Assess for airway symptoms (snoring, stridor, apnea, respiratory distress).	W/wakefulness, sleep, & feeding
	Overnight polysomnography (sleep study)	To identify & quantify degree of sleep apnea
	Consider consultation w/otolaryngologist & sleep medicine specialist.	Airway endoscopy (flexible bedside endoscopy; diagnostic laryngoscopy & bronchoscopy) may help identify types & degree of airway narrowing.
Musculoskeletal	CT scan of head/skull/sutures	CT w/3D reconstruction will delineate suture involvement & guide preoperative planning.
	Cervical spine imaging to evaluate for vertebral fusions & instability, which may also manifest as scoliosis	CT of cervical spine before any surgery, & if abnormal, consultation w/spine expert to delineate spine precautions. Or perform radiograph after age 2 yrs (when vertebrae are ossified).
	Hand radiographs to evaluate extent of syndactyly (commonly incl bony fusion) or symphalangism	Consultation w/hand surgeon & hand therapist
Gastrointestinal	Upper GI w/small-bowel follow-through if symptomatic or during preoperative eval for gastrostomy tube	To evaluate for intestinal malrotation
Neurologic	CT scan or MRI of the head to evaluate for hydrocephalus & CNS anomalies. Monitor head growth closely.	Consider brain MRI if concern for hydrocephalus or Chiari I malformation.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Development	Assessment for developmental disabilities	Referral for early intervention services. Consider referral to a neurodevelopmental specialist.
Cardiovascular	Cardiac assessment	Echocardiogram if murmur present or if clinical cardiac concerns
Genitourinary	Assessment for cryptorchidism in males	If present, referral to urologist
	Renal ultrasound	To evaluate for hydronephrosis
Other	Consultation w/clinical geneticist & genetic counselor	To incl recurrence risk counseling

CNS = central nervous system

Treatment of Manifestations

Individuals with an *FGFR* craniosynostosis syndrome benefit from a multidisciplinary craniofacial team approach including plastic surgeons, neurosurgeons, otolaryngologists, dentists, audiologists, speech pathologists, developmental pediatricians, social workers, and clinical geneticists. Note: For recommended treatment of manifestations of Muenke syndrome, see [Muenke Syndrome](#).

Table 5. Treatment of Manifestations in Individuals with *FGFR* Craniosynostosis Syndromes

Manifestation/Concern	Treatment	Considerations/Other
Craniosynostosis	In general, multisuture craniosynostosis should be surgically repaired in 1st yr of life. 1, 2, 3, 4	Specific timing guided by child's anatomy, risk for ↑ intracranial pressure, & respiratory status 5
Midface retrusion	Jaw surgery to advance the midface	<ul style="list-style-type: none"> Typically in childhood or adolescence 6, 7 Early midface advancement may be pursued to treat airway obstruction.
Cleft palate	Palate surgery is typically performed prior to development of pressure consonants.	To improve speech production & intelligibility
Feeding/swallowing difficulties 8	Feeding therapy is helpful to assess swallowing safety & support eating by mouth.	Swallowing is formally assessed after craniofacial surgeries.
Dental	Pediatric dental care & eval by craniofacial orthodontist as part of coordinated craniofacial team care	Orthodontist plays an important role in determining type & timing of orthodontic & orthognathic interventions.
Strabismus	Strabismus should be treated by ophthalmologist w/expertise in eye alignment in children w/craniosynostosis.	Amblyopia is a major cause of visual impairment.
Proptosis	Early initiation of topical eye lubrication if inadequate lid closure	Tarsorrhaphy may be indicated, e.g., w/globe subluxation or to prevent globe luxation &/or exposure keratopathy.
Hearing loss	Placement of tympanostomy tubes	If chronic middle ear effusions are present
	Hearing aids, bone conduction sound processors, tympanoplasties, & aural atresia/stenosis repair	Optimization of hearing facilitates language & communication development.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Airway obstruction	Awareness of potential airway compromise & proactive airway management are crucial in infants & children.	<ul style="list-style-type: none"> • Specific airway management depends on level & severity of obstruction. • Residual OSA after soft tissue & skeletal procedures is common.
	Temporizing measures to bypass airway obstruction: <ul style="list-style-type: none"> • Placement of nasal stents • Endotracheal intubation • Tracheotomy 	Infants & children requiring tracheotomy may also need ventilator-delivered positive pressure to normalize gas exchange & achieve normal sleep & growth. ⁸
Sleep apnea	Surgical interventions (adenoidectomy, nasal airway procedures, tracheostomy) are often helpful.	Avoid use of CPAP/BiPAP for long-term treatment of sleep apnea when possible, as pressure on midface exacerbates midface retrusion.
	Supplemental oxygen via nasal cannula is sometimes beneficial.	Reducing sleep apnea & improving sleep quality may improve learning, cognition, & behavior.
Syndactyly	Type & timing of surgeries depends on presence of thumb syndactyly & extent of soft tissue deficiency.	A common goal: improve hand & foot function w/smallest number of surgeries
	Treatment can be separated into early phase (syndactyly releases) & late phases (functional osteotomies). ^{9, 10}	Most individuals require multiple procedures & revisions throughout childhood. ¹¹
Malrotation	Standard treatment per surgeon	Upper GI series prior to gastrostomy tube placement
Speech abnormalities	Speech eval by speech-language pathologist w/craniofacial expertise to guide speech therapy recommendations	Articulation, resonance, language development, & intelligibility may be affected.
Developmental delay	Early intervention services	Consider consultation w/developmental pediatrician or neurodevelopmental specialist.
Congenital heart defects	Standard treatment per cardiologist	Consider preoperative closure of intra-cardiac shunts to ↓ embolic risk before synostosis surgery.
Cryptorchidism in males or hydronephrosis	Standard treatment per urologist	
Scoliosis	Standard treatment per orthopedist	
Acne	Oral isotretinoin may be considered for those w/refractory acne not responsive to standard therapies. ¹²	Oral isotretinoin is a known human teratogen & should not be prescribed to females of childbearing age unless 2 independent forms of birth control are instituted & monthly pregnancy tests performed.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Emotional & behavioral adjustment	Psychosocial assessments & mental health support throughout childhood ¹³	Recognize & address potential bullying/teasing by peers.

OSA = obstructive sleep apnea

1. Cranioplasty involves release of fused sutures and repositioning and reconstruction of the calvaria, in order to prevent increased intracranial pressure and reduce progressive abnormal craniofacial development.
2. Several techniques including endoscopic strip craniectomy, advancement through posterior distraction, and traditional cranioplasty are in current use. It is important to delay traditional anterior cranial fronto-orbital advancement until as late as possible in syndromic cases because of a high rate of relapse when done at early ages. Thus, early posterior cranial expansion can be used early in life to minimize progression of the anterior deformity. Early distraction osteogenesis can be a temporizing measure to allow subsequent traditional surgeries to be performed at a favorable age [Hopper 2012].
3. Early surgery may be performed to reduce intracranial pressure; however, young infants with Apert syndrome may have minimal physiologic reserve, which may affect surgical outcomes. Later surgeries tend to lead to a more stable bony correction [Taylor & Bartlett 2016].
4. A staged approach to increase intracranial volume and protect the globes is often pursued, and most children with bicoronal craniosynostosis benefit from a fronto-orbital advancement.
5. The goals of craniofacial surgery are to provide adequate intracranial volume to allow brain development and to improve head shape. The timing and sequence of surgical interventions are dependent on the individual's functional, aesthetic, and psychological needs [McCarthy et al 2012].
6. Timing of jaw surgery is guided by the affected individual's occlusion and degree of airway obstruction.
7. Compared with Le Fort III distraction, Le Fort II distraction with simultaneous repositioning of the zygomas improves the facial and orbital relationships for older children with Apert syndrome [Hopper et al 2013].
8. Serious caution must be taken in the placement and care of tracheostomies in individuals with tracheal cartilaginous sleeves because of abnormal tissue healing and granulation tissue formation [Wenger et al 2017].
9. Fearon & Rhodes [2009]
10. Recent studies describe novel techniques to improve aesthetic outcomes in children with complex syndactylies [Lohmeyer et al 2016].
11. Pettitt et al [2017]
12. Evidence suggests that oral isotretinoin may be more effective than standard therapies, and biologic models support a role for isotretinoin in regulating androgens and *FGFR2* signaling [Melnik et al 2009].
13. Suggested areas of focus include the parents' and family's emotional, social, and financial needs; the child's neurocognitive development and educational needs; and potential barriers to care [McCarthy et al 2012].

Surveillance

Note: (1) For recommended surveillance for Muenke syndrome, see [Muenke Syndrome](#). (2) For additional surveillance recommendations specific to Apert syndrome, see [Apert Syndrome](#).

Table 6. Recommended Surveillance for Individuals with *FGFR* Craniosynostosis Syndromes

System/Concern	Evaluation	Frequency
Hydrocephalus	<ul style="list-style-type: none"> • Close monitoring of head circumference / head growth • Eval for signs of ↑ intracranial pressure (e.g., headaches, vomiting) 	Clinical eval at least every 3 mos in 1st year of life; can be done in conjunction w/team visits to assess for craniosynostosis
	Ophthalmologic exam for papilledema	At least annually, & w/any concerning symptoms
Cervical spine instability	Cervical spine x-rays &/or CT cervical spine	<ul style="list-style-type: none"> • Consider cervical spine CT when head CT is obtained. • Consider x-rays at age 3-4 yrs to evaluate for progressive C-spine fusion.

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Tracheal anomalies	Operative airway eval	At the time of 1st anesthesia, performed by otolaryngologist. Craniofacial otolaryngologist should direct timing of operative airway eval if no sedation is planned, but eval should occur in infancy because of risk of sudden death if tracheal cartilaginous sleeve is present.
Dental issues	Eval by craniofacial orthodontist	When secondary teeth erupt
Vision issues	Ophthalmologic exam of optic nerves; eval for sclerocornea, orbital protection, strabismus &/or amblyopia	At least annually, & urgently if any concern arises
Hearing loss	Audiology eval	At least annually
Sleep apnea	Clinical eval for symptoms of sleep apnea	At least every 3 mos in 1st year & annually thereafter
	Polysomnography	As indicated by clinical symptoms; if central apnea present, consider brain MR exam to evaluate for Chiari I malformation.
Speech issues	Speech pathology eval	<ul style="list-style-type: none"> At age ~18 mos, then annually Additional speech assessments before & after midface surgeries
Neurodevelopment	Early intervention &/or neurodevelopmental pediatrics eval	At least every 3 mos in 1st yr & annually thereafter

Agents/Circumstances to Avoid

Individuals with cervical spine anomalies may be at risk for spinal cord injury with hyperextension and may require fiberoptic intubation and/or sports restrictions for activities that pose a risk for head/neck injury.

Individuals with exophthalmos may require protective eyewear during activities with risk of eye injury (e.g., ball sports).

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from who would benefit from early surveillance and intervention. Evaluations can include the following:

- Molecular genetic testing if the *FGFR* pathogenic variant in the family is known
- Assessment based on clinical and radiographic criteria (Note: Manifestations may not be readily evident in all affected individuals.)

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Pregnant women carrying fetuses affected by *FGFR* craniosynostosis syndromes should be monitored during pregnancy for features that can affect early morbidity and mortality, and should be encouraged to deliver in a hospital with ready access to pediatric otolaryngology, plastic surgery, neurosurgery, and pulmonary medicine. Because of the high rate of respiratory obstruction such as choanal atresia, a health care provider skilled in endotracheal intubation and resuscitation should be present at the delivery.

See [MotherToBaby](#) for further information on medication use during pregnancy.

Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Chapter Notes

Author History

Kelly Evans, MD (2020-present)

Marnie J Falk, MD; Children's Hospital of Philadelphia (1998-2020)

Chad R Haldeman-Englert, MD; Fullerton Genetics Center (2007-2020)

Danny Miller, MD, PhD (2020-present)

Nathaniel H Robin, MD; University of Alabama at Birmingham (1998-2020)

Tara Wenger, MD, PhD (2020-present)

Revision History

- 30 April 2020 (tw) Revision: clarification regarding syndactyly/polydactyly in Apert syndrome
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- 18 April 2005 (me) Comprehensive update posted live
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References

Literature Cited

- Aravidis C, Konialis CP, Pangalos CG, Kosmaidou Z. A familial case of Muenke syndrome. Diverse expressivity of the FGFR3 Pro252Arg mutation – case report and review of the literature. *J Matern Fetal Neonatal Med.* 2014;27:1502–6. PubMed PMID: 24168007.
- Barbosa M, Almeida Mdo R, Reis-Lima M, Pinto-Basto J, dos Santos HG. Muenke syndrome with osteochondroma. *Am J Med Genet.* 2009;149A:260–1. PubMed PMID: 19097163.
- Bessenyei B, Tihanyi M, Hartwig M, Szakszon K, Oláh É. Variable expressivity of Pfeiffer syndrome in a family with FGFR1 p.Pro252Arg mutation. *Am J Med Genet A.* 2014;164A:3176–9. PubMed PMID: 25251565.
- Bissacotti Steglich EM, Steglich RB, Melo MM, de Almeida HL Jr. Extensive acne in Apert syndrome. *Int J Dermatol.* 2016;55:e596–8. PubMed PMID: 27428282.
- Bochukova EG, Roscioli T, Hedges DJ, Taylor IB, Johnson D, David DJ, Deininger PL, Wilkie AO. Rare mutations of FGFR2 causing Apert syndrome: identification of the first partial gene deletion, and an Alu element insertion from a new subfamily. *Hum Mutat.* 2009;30:204–11. PubMed PMID: 18726952.
- Bracero LA, Clark D, Pieffer M, Fakhry J. Sonographic findings in a case of cloverleaf skull deformity and prune belly. *Am J Perinatol.* 1988;5:239–41. PubMed PMID: 3289554.
- Breik O, Mahindu A, Moore MH, Molloy CJ, Santoreneos S, David DJ. Central nervous system and cervical spine abnormalities in Apert syndrome. *Childs Nerv Syst.* 2016;32:833–8. PubMed PMID: 26861132.

- Bulfamante G, Gana S, Avagliano L, Fabietti I, Gentilin B, Lalatta F. Congenital diaphragmatic hernia as prenatal presentation of Apert syndrome. *Prenat Diagn*. 2011;31:910–1. PubMed PMID: 21706505.
- Choi SK, Yoon SR, Calabrese P, Arnheim N. A germ-line-selective advantage rather than an increased mutation rate can explain some unexpectedly common human disease mutations. *Proc Natl Acad Sci USA*. 2008;105:10143–8. PubMed PMID: 18632557.
- Cinalli G, Renier D, Sebag G, Sainte-Rose C, Arnaud E, Pierre-Kahn A. Chronic tonsillar herniation in Crouzon's and Apert's syndromes: the role of premature synostosis of the lambdoid suture. *J Neurosurg*. 1995;83:575–82. PubMed PMID: 7674004.
- Cinalli G, Sainte-Rose C, Kollar EM, Zerah M, Brunelle F, Chumas P, Arnaud E, Marchac D, Pierre-Kahn A, Renier D. Hydrocephalus and craniosynostosis. *J Neurosurg*. 1998;88:209–14. PubMed PMID: 9452225.
- Cohen MM Jr, Kreiborg S. Visceral anomalies in the Apert syndrome. *Am J Med Genet*. 1993;45:758–60. PubMed PMID: 8456856.
- Cohen MM, Kreiborg S. Hand and feet in the Apert syndrome. *Am J Med Genet*. 1995;57:82–96. PubMed PMID: 7645606.
- Coll G, Sakka L, Botella C, Pham-Dang N, Collet C, Zerah M, Arnaud E, Di Rocco F. Pattern of closure of skull base synchondroses in Crouzon syndrome. *World Neurosurg*. 2018;109:e460–7. PubMed PMID: 29024761.
- Driessen C, Joosten KF, Bannink N, Bredero-Boelhouwer HH, Hoeve HL, Wolvius EB, Rizopoulos D, Mathijssen IM. How does obstructive sleep apnoea evolve in syndromic craniosynostosis? A prospective cohort study. *Arch Dis Child*. 2013;98:538–43. PubMed PMID: 23702437.
- Fearon JA, Rhodes J. Pfeiffer syndrome: a treatment evaluation. *Plast Reconstr Surg*. 2009;123:1560–9. PubMed PMID: 19407629.
- Fenwick AL, Bowdin SC, Klatt REM, Wilkie AOM. A deletion of FGFR2 creating a chimeric IIIb/IIIc exon in a child with Apert syndrome. *BMC Med Genet*. 2011;12:122. PubMed PMID: 21943124.
- Fischer S, Tovetjam R, Maltese G, Sahlin PE, Tarnow P, Kolby L. Psychosocial conditions in adults with Crouzon syndrome: a follow-up study of 31 Swedish patients. *J Plast Surg Hand Surg*. 2014;48:244–7. PubMed PMID: 24328900.
- Flöttmann R, Knaus A, Zemojtel T, Robinson PN, Mundlos S, Horn D, Spielmann M. FGFR2 mutation in a patient without typical features of Pfeiffer syndrome – the emerging role of combined NGS and phenotype based strategies. *Eur J Med Genet*. 2015;58:376–80. PubMed PMID: 26096994.
- Forte AJ, Alonso N, Persino JA, Pfaff MJ, Brooks ED, Steinbacher EM. Analysis of midface retrusion in Crouzon and Apert syndromes. *Plast Reconstr Surg*. 2014;134:285–93. PubMed PMID: 25068327.
- Glaser RL, Jiang W, Boyadjiev SA, Tran AK, Zachary AA, Van Maldergem L, Johnson D, Walsh S, Oldridge M, Wall SA, Wilkie AO, Jabs EW. Paternal origin of FGFR2 mutations in sporadic cases of Crouzon syndrome and Pfeiffer syndrome. *Am J Hum Genet*. 2000;66:768–77. PubMed PMID: 10712195.
- Goriely A, McVean GA, Rojmyr M, Ingemarsson B, Wilkie AO. Evidence for selective advantage of pathogenic FGFR2 mutations in the male germ line. *Science*. 2003;301:643–6. PubMed PMID: 12893942.
- Goriely A, Lord H, Lim J, Johnson D, Lester T, Firth HV, Wilkie AO. Germline and somatic mosaicism for FGFR2 mutation in the mother of a child with Crouzon syndrome: implications for genetic testing in "paternal age-effect" syndromes. *Am J Med Genet*. 2010;152A:2067–73. PubMed PMID: 20635358.
- Helfer TM, Peixoto AB, Tonni G, Junior EA. Craniosynostosis: prenatal diagnosis by 2D/3D ultrasound, magnetic resonance imaging and computed tomography. *Med Ultrason*. 2016;18:378–85. PubMed PMID: 27622416.
- Hibberd CE, Bowdin S, Arudchelvan Y, Forrest CR, Brakora KA, Marcucio RS, Gong SG. FGFR-associated craniosynostosis syndromes and gastrointestinal defects. *Am J Med Genet A*. 2016;170:3215–21. PubMed PMID: 27481450.

- Honnebier MB, Cabiling DS, Hetlinger M, McDonald-McGinn DM, Zackai EH, Bartlett SP. The natural history of patients treated for FGFR3-associated (Muenke-type) craniosynostosis. *Plast Reconstr Surg*. 2008;121:919–31. PubMed PMID: 18317141.
- Hopper RA. New trends in cranio-orbital and midface distraction for craniofacial dysostosis. *Curr Opin Otolaryngol Head Neck Surg*. 2012;20:298–303. PubMed PMID: 22894998.
- Hopper RA, Kapadia H, Morton T. Normalizing facial ratios in Apert syndrome patients with Le Fort II midface distraction and simultaneous zygomatic repositioning. *Plast Reconstr Surg*. 2013;132:129–40. PubMed PMID: 23508053.
- Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. *J Community Genet*. 2022;13:389–97. PubMed PMID: 35834113.
- Hunt CE, Puczynski MS. Does supine sleeping cause asymmetric heads? *Pediatrics*. 1996;98:127–9. PubMed PMID: 8668385.
- Jehee FS, Alonso LG, Cavalcanti DP, Kim C, Wall SA, Mulliken JB, Sun M, Jabs EW, Boyadjiev SA, Wilkie AO, Passos-Bueno MR. Mutational screening of FGFR1, CER1, and CDON in a large cohort of trigonocephalic patients. *Cleft Palate Craniofac J*. 2006;43:148–51. PubMed PMID: 16526918.
- Kane AA, Mitchell LE, Craven KP, Marsh JL. Observations on a recent increase in plagiocephaly without synostosis. *Pediatrics*. 1996;97:877–85. PubMed PMID: 8657530.
- Kaur R, Mishra P, Kumar S, Sankar MJ, Kabra M, Gupta N. Apert syndrome with congenital diaphragmatic hernia: another case report and review of the literature. *Clin Dysmorphol*. 2019;28:78–80. PubMed PMID: 30672749.
- Ketwaroo PD, Robson C, Estroff JA. Prenatal imaging of craniosynostosis syndromes. *Semin Ultrasound CT MR*. 2015;36:453–64. PubMed PMID: 26614129.
- Kolar JC, Dithakasem K, Fearon JA. Long-term evaluation of mandibular growth in children with FGFR2 mutations. *J Craniofac Surg*. 2017;28:709–12. PubMed PMID: 28468153.
- Kosiński P, Luterek K, Wielgoś M. Diaphragmatic hernia as an early ultrasound manifestation of Apert syndrome. *Ginekol Pol*. 2016;87:830. PubMed PMID: 28098935.
- Klopocki E, Lohan S, Brancati F, Koll R, Brehm A, Seemann P, Dathe K, Stricker S, Hecht J, Bosse K, Betz RC, Garaci FG, Dallapiccola B, Jain M, Muenke M, Ng VC, Chan W, Chan D, Mundlos S. Copy-number variations involving the IHH locus are associated with syndactyly and craniosynostosis. *Am J Hum Genet*. 2011;88:70–5. PubMed PMID: 21167467.
- Lai AH, Tan YM, Law HY, Yeow VK. A mutation in FGFR2 in a child with Pfeiffer syndrome and a sacral appendage. *Clin Dysmorphol*. 2008;17:73–4. PubMed PMID: 18049087.
- Lapunzina P, Fernandez A, Sanchez Romero JM, Delicado A, Saenz de Pipaon M, Lopez Pajares I, Molano J. A novel insertion in the FGFR2 gene in a patient with Crouzon phenotype and sacrococcygeal tail. *Birth Defects Res A Clin Mol Teratol*. 2005;73:61–4. PubMed PMID: 15602758.
- LeBlanc S, David D, Colley A, Buckley M, Roscioli T, Barnett C. Atypical skin manifestations in FGFR2-related craniosynostosis syndromes broaden the phenotypic spectrum. *Mol Syndromol*. 2018;9:149–53. PubMed PMID: 29928180.
- Lin M, Lu Y, Siu Y, Zhao N, Jin Y, Yi D, Jiang M. Extremely severe scoliosis, heterotopic ossification, and osteoarthritis in a three-generation family with Crouzon syndrome carrying a mutant c.799T>C FGFR2. *Mol Genet Genomic Med*. 2019;7:e843. PubMed PMID: 31318164.
- Lohmeyer JA, Hülsemann W, Mann M, Habenicht R. Transverse soft tissue distraction preceding separation of complex syndactylies. *J Hand Surg Eur Vol*. 2016;41:308–14. PubMed PMID: 26497594.

- Mantilla-Capacho JM, Arnaud L, Diaz-Rodriguez M, Barros-Nunez P. Apert syndrome with preaxial polydactyly showing the typical mutation Ser252Trp in the FGFR2 gene. *Genet Couns*. 2005;16:403–6. PubMed PMID: 16440883.
- Mathijssen IM. Guideline for care of patients with the diagnosis of craniosynostosis: working group on craniosynostosis. *J Craniofac Surg*. 2015;26:1735–807. PubMed PMID: 26355968.
- McCann E, Kaye SB, Newman W, Norbury G, Black GCM, Ellis IH. Novel phenotype of craniosynostosis and ocular anterior chamber dysgenesis with a fibroblast growth factor receptor 2 mutation. *Am J Med Genet A*. 2005;138A:278–81. PubMed PMID: 16158432.
- McCarthy JG, Warren SM, Bernstein J, Burnett W, Cunningham ML, Edmond JC, Figueroa AA, Kapp-Simon KA, Labow BI, Peterson-Falzone SJ, Proctor MR, Rubin MS, Sze RW, Yemen TA, et al. Parameters of care for craniosynostosis. *Cleft Palate Craniofac J*. 2012;49:1S–24S. PubMed PMID: 21848431.
- Melnik BC, Schmitz G, Zouboulis CC. Anti-acne agents attenuate FGFR2 signal transduction in acne. *J Invest Dermatol*. 2009;129:1868–77. PubMed PMID: 19225542.
- Merrill AE, Sarukhanov A, Krejci P, Idoni B, Camacho N, Estrada KD, Lyons KM, Deixler H, Robinson H, Chitayat D, Curry CJ, Lachman RS, Wilcox WR, Deborah Krakow D. Bent bone dysplasia-FGFR2 type, a distinct skeletal disorder, has deficient canonical FGF signaling. *Am J Hum Genet*. 2012;90:550–7. PubMed PMID: 22387015.
- Moko SB, Blandin de Chalain TM. New Zealand Maori family with the Pro250Arg fibroblast growth factor receptor 3 mutation associated with craniosynostosis. *J Craniomaxillofac Surg*. 2001;29:22–4. PubMed PMID: 11467490.
- Moloney DM, Slaney SF, Oldridge M, Wall SA, Sahlin P, Stenman G, Wilkie AO. Exclusive paternal origin of new mutations in Apert syndrome. *Nat Genet*. 1996;13:48–53. [see comments]. PubMed PMID: 8673103.
- Muenke M, Gripp KW, McDonald-McGinn DM, Gaudenz K, Whitaker LA, Bartlett SP, Markowitz RI, Robin NH, Nwokoro N, Mulvihill JJ, Losken HW, Mulliken JB, Guttmacher AE, Wilroy RS, Clarke LA, Hollway G, Ades LC, Haan EA, Mulley JC, Cohen MM Jr, Bellus GA, Francomano CA, Moloney DM, Wall SA, Wilkie AO. A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) defines a new craniosynostosis syndrome. *Am J Hum Genet*. 1997;60:555–64. PubMed PMID: 9042914.
- Mulliken JB, Steinberger D, Kunze S, Muller U. Molecular diagnosis of bilateral coronal synostosis. *Plast Reconstr Surg*. 1999;104:1603–15. PubMed PMID: 10541159.
- Murdoch-Kinch CA, Ward RE. Metacarpophalangeal analysis in Crouzon syndrome: additional evidence for phenotypic convergence with the acrocephalosyndactyly syndromes. *Am J Med Genet*. 1997;73:61–6. PubMed PMID: 9375924.
- Oldridge M, Zackai EH, McDonald-McGinn DM, Iseki S, Morriss-Kay GM, Twigg SR, Johnson D, Wall SA, Jiang W, Theda C, Jabs EW, Wilkie AO. De novo alu-element insertions in FGFR2 identify a distinct pathological basis for Apert syndrome. *Am J Hum Genet*. 1999;64:446–61. PubMed PMID: 9973282.
- Oliveira NA, Alonso LG, Fanganiello RD, Passos-Bueno MR. Further evidence of association between mutations in FGFR2 and syndromic craniosynostosis with sacrocoxygeal eversion. *Birth Defects Res A Clin Mol Teratol*. 2006;76:629–33. PubMed PMID: 16955501.
- Pelz L, Unger K, Radke M. Esophageal stenosis in acrocephalosyndactyly type I. *Am J Med Genet*. 1994;53:91. PubMed PMID: 7802047.
- Peña-Padilla C, Viramontes-Aguilar L, Tavares-Macias G, Bobadilla-Morales L, Cunningham ML, Park S, Zapata-Aldana E, Corona-Rivera JR. Pfeiffer syndrome Type 3 and prune belly anomaly in a female: case report and review. *Fetal Pediatr Pathol*. 2019;38:412–7. PubMed PMID: 31002276.
- Pettitt DA, Arshad Z, Mishra A, McArthur P. Apert syndrome: a consensus on the management of Apert hands. *J Craniomaxillofac Surg*. 2017;45:223–31. PubMed PMID: 28087285.

- Pickrell BB, Meaie JD, Canadas KT, Chandy BM, Buchanan EP. Tracheal cartilaginous sleeve in syndromic craniosynostosis: an underrecognized source of significant morbidity and mortality. *J Craniofac Surg*. 2017;28:696–9. PubMed PMID: 28468151.
- Rannan-Eliya SV, Taylor IB, De Heer IM, Van Den Ouweland AM, Wall SA, Wilkie AO. Paternal origin of FGFR3 mutations in Muenke-type craniosynostosis. *Hum Genet*. 2004;115:200–7. PubMed PMID: 15241680.
- Reitsma JH, Balk-Leurs IH, Ongkosuwito EM, Wattel E, Prahl-Andersen B. Dental maturation in children with the syndrome of Crouzon and Apert. *Cleft Palate Craniofac J*. 2014;51:639–44. PubMed PMID: 24021057.
- Renier D, Arnaud E, Cinalli G, Sebag G, Zerah M, Marchac D. Prognosis for mental function in Apert's syndrome. *J Neurosurg*. 1996;85:66–72. PubMed PMID: 8683284.
- Rijken BF, Lequin MH, Van Veelen ML, de Rooi J, Mathijssen IM. The formation of the foramen magnum and its role in developing ventriculomegaly and Chiari I malformation in children with craniosynostosis syndromes. *J Craniomaxillofac Surg*. 2015;43:1042–8. PubMed PMID: 26051848.
- Robin NH, Segel B, Carpenter G, Muenke M. Craniosynostosis, Philadelphia type: a new autosomal dominant syndrome with sagittal craniosynostosis and syndactyly of the fingers and toes. *Am J Med Genet*. 1996;62:184–91. PubMed PMID: 8882401.
- Rossi M, Jones RL, Norbury G, Bloch-Zupan A, Winter RM. The appearance of the feet in Pfeiffer syndrome caused by FGFR1 P252R mutation. *Clin Dysmorphol*. 2003;12:269–74. PubMed PMID: 14564217.
- Rouzier C, Soler C, Hofman P, Brennetot C, Bieth E, Pedeutour F. Ovarian dysgerminoma and Apert syndrome. *Pediatr Blood Cancer*. 2008;50:696–8. PubMed PMID: 17243131.
- Rymer K, Shiang R, Hsiung A, Pandya A, Bigdeli T, Webb BT, Rhodes J. Expanding the phenotype for the recurrent p.Ala391Glu variant in FGFR3: beyond Crouzon syndrome and acanthosis nigricans. *Mol Genet Genomic Med*. 2019;7:e656. PubMed PMID: 31016899.
- Shotelersuk V, Ittiwut C, Srivuthana S, Mahatumarat C, Lerdlum S, Wacharsindhu S. Distinct craniofacial-skeletal-dermatological dysplasia in a patient with W290C mutation in FGFR2. *AJMG. Am J Med Genet*. 2002;113:4–8. PubMed PMID: 12400058.
- Slavotinek A, Crawford H, Golabi M, Tao C, Perry H, Oberoi S, Vargervik K, Friez M. Novel FGFR2 deletion in a patient with Beare-Stevenson-like syndrome. *Am J Med Genet A*. 2009;149A:1814–7. PubMed PMID: 19610084.
- Sobaih BH, AlAli AA. A third report of Apert syndrome in association with diaphragmatic hernia. *Clin Dysmorphol*. 2015;24:106–8. PubMed PMID: 25714562.
- Stoler JM, Rosen H, Desai U, Mulliken JB, Meara JG, Rogers GF. Cleft palate in Pfeiffer syndrome. *J Craniofac Surg*. 2009;20:1375–7. PubMed PMID: 19816260.
- Taylor JA, Bartlett SP. Discussion: first vault expansion in Apert and Crouzon-Pfeiffer syndromes: front or back? *Plast Reconstr Surg*. 2016;137:122e–4e. PubMed PMID: 26710016.
- Tonni G, Panteghini M, Rossi A, Baldi M, Magnani C, Ferrari B, Lituania M. Craniosynostosis: prenatal diagnosis by means of ultrasound and SSSE-MRI. Family series with report of neurodevelopmental outcome and review of the literature. *Arch Gynecol Obstet*. 2011;283:909–16. PubMed PMID: 20811900.
- Wenger TL, Dahl J, Bhoj EJ, Rosen A, McDonald-McGinn D, Zackai E, Jacobs I, Heike CL, Hing A, Santani A, Inglis AF, Sie KC, Cunningham M, Perkins J. Tracheal cartilaginous sleeves in children with syndromic craniosynostosis. *Genet Med*. 2017;19:62–8. PubMed PMID: 27228464.
- Wenger TL, Hopper RA, Rosen A, Tully HM, Cunningham ML, Lee A. A genotype-specific surgical approach for patients with Pfeiffer syndrome due to W290C pathogenic variant in FGFR2 is associated with improved developmental outcomes and reduced mortality. *Genet Med*. 2019;21:471–6. PubMed PMID: 29915381.

- Wilkie AO, Byren JC, Hurst JA, Jayamohan J, Johnson D, Knight SJ, Lester T, Richards PG, Twigg SR, Wall SA. Prevalence and complications of single-gene and chromosomal disorders in craniosynostosis. *Pediatrics*. 2010;126:e391–400. PubMed PMID: 20643727.
- Wilkie AO, Slaney SF, Oldridge M, Poole MD, Ashworth GJ, Hockley AD, Hayward RD, David DJ, Pulleyn LJ, Rutland P, Malcolm S, Winter RM, Reardon W. Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. *Nature Genet*. 1995;9:165–72. PubMed PMID: 7719344.
- Witters I, Devriendt K, Moerman P, van Hole C, Fryns JP. Diaphragmatic hernia as the first echographic sign in Apert syndrome. *Prenat Diagn*. 2000;20:404–6. PubMed PMID: 10820409.
- Xu W, McDonald-McGinn DM, Melchiorre AJ, Zackai EH, Bartlett SP, Taylor JA. Crouzon with acanthosis nigricans and odontogenic tumors: a rare form of syndromic craniosynostosis. *Cleft Palate Craniofac J*. 2018;55:296–300. PubMed PMID: 29351036.
- Yoon SR, Qin J, Glaser RL, Jabs EW, Wexler NS, Sokol R, Arnheim N, Calabrese P. The ups and downs of mutation frequencies during aging can account for the Apert syndrome paternal age effect. *PLoS Genet*. 2009;5:e1000558. PubMed PMID: 19593369.
- Zarate YA, Putnam PE, Saal HM. Intestinal malrotation in a patient with Pfeiffer syndrome type 2. *Cleft Palate Craniofac J*. 2010;47:638–41. PubMed PMID: 20509766.

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