U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Wenger TL, Hing AV, Evans KN. Apert Syndrome. 2019 May 30. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Apert Syndrome

Synonym: Acrocephalosyndactyly Type I

Tara L Wenger, MD, PhD,[1] Anne V Hing, MD,[1] and Kelly N Evans, MD[1]

Created: May 30, 2019.

Summary

Clinical characteristics

Apert syndrome is characterized by the presence of multisuture craniosynostosis, midface retrusion, and syndactyly of the hands with fusion of the second through fourth nails. Almost all affected individuals have coronal craniosynostosis, and a majority also have involvement of the sagittal and lambdoid sutures. The midface in Apert syndrome is underdeveloped as well as retruded; a subset of affected individuals have cleft palate. The hand in Apert syndrome always includes fusion of the middle three digits; the thumb and fifth finger are sometimes also involved. Feeding issues, dental abnormalities, hearing loss, hyperhidrosis, and progressive synostosis of multiple bones (skull, hands, feet, carpus, tarsus, and cervical vertebrae) are also common. Multilevel airway obstruction may be present and can be due to narrowing of the nasal passages, tongue-based airway obstruction, and/or tracheal anomalies. Nonprogressive ventriculomegaly is present in a majority of individuals, with a small subset having true hydrocephalus. Most individuals with Apert syndrome have normal intelligence or mild intellectual disability; moderate-to-severe intellectual disability has been reported in some individuals. A minority of affected individuals have structural cardiac abnormalities, true gastrointestinal malformations, and anomalies of the genitourinary tract.

Diagnosis/testing

The diagnosis of Apert syndrome is established in a proband with classic clinical characteristics (multisuture craniosynostosis, midface retrusion, and syndactyly) and/or by the identification of a heterozygous pathogenic variant in *FGFR2* by molecular genetic testing AND phenotypic features consistent with Apert syndrome.

Management

Treatment of manifestations: Management by a craniofacial team is ideal. In general, multisutural craniosynostosis should be surgically repaired in the first year of life; jaw surgery to advance the midface often occurs in childhood and adolescence. Cleft palate repair may be performed prior to the development of pressure consonants. Feeding therapy is often helpful. Pediatric dental care is recommended. Treatment of strabismus

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

should be performed by an ophthalmologist with expertise in eye alignment in children with craniosynostosis. Hearing aids may be required for hearing loss. If airway obstruction is present, temporizing measures may be required. Treatment of sleep apnea by surgical intervention and/or supplemental oxygen via nasal cannula may be required. The type and timing of surgical repair for syndactyly depends on the presence of thumb syndactyly and extent of soft tissue deficiency. Early intervention services for speech abnormalities and developmental delay should be initiated. Standard treatment of congenital heart defects, malrotation, cryptorchidism in males, hydronephrosis, acne, and scoliosis should be instituted when appropriate.

Prevention of secondary complications: Timely surgical treatment of craniosynostosis may prevent increased intracranial pressure that can lead to papilledema and cognitive impairment; ocular lubricants to prevent exposure keratopathy and corneal scarring; anesthesia evaluation before any surgical intervention to prevent perioperative respiratory complications; spine precautions and consultation with a spine surgeon to prevent spinal cord injury and neurologic sequelae in those with cervical spine anomalies. Clinical feeding evaluation and/or video fluoroscopic swallow study is needed to determine if precautions are required to prevent aspiration pneumonia and subsequent chronic lung disease.

Surveillance: Measurement of head circumference and fontanelle size and assessment for increased intracranial pressure at each appointment in infancy and early childhood; assessment of developmental progress at each visit; evaluation by a craniofacial team regularly in infancy, childhood, and adolescence; dental care every six months; assessment for velopharyngeal insufficiency after emergence of language; assessment for speech disorders, ophthalmologic evaluation, and audiologic/otologic assessments at least annually; evaluation for the development of scoliosis annually in childhood and adolescence.

Agents/circumstances to avoid: Contact sports and activities that involve neck hyperflexion or extension for those with cervical spine anomalies; factors that potentiate hearing loss; use of CPAP/BiPAP for long-term treatment of sleep apnea.

Pregnancy management: For affected pregnant women: monitoring for signs and symptoms of worsening obstructive sleep apnea and anethesia evaluation prior to initiation of labor to identify any multilevel airway anomalies or vertebral anomalies that would result in additional risk with certain types of anesthesia; fiberoptic intubation could be required.

Genetic counseling

Apert syndrome is inherited in an autosomal dominant manner. However, most individuals with Apert syndrome have the disorder as the result of a *de novo FGFR2* pathogenic variant. Advanced paternal age has been shown to be associated with *de novo* pathogenic variants for Apert syndrome. Affected individuals have a 50% chance of passing the pathogenic variant to each child. Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant has been identified in the family.

Diagnosis

Consensus clinical diagnostic criteria for Apert syndrome have not been published.

Suggestive Findings

Apert syndrome **should be suspected** in individuals with the following clinical features.

Head

- Multisuture craniosynostosis, most commonly involving bilateral coronal sutures with variable involvement of the remaining cranial sutures

- Midface retrusion with a greater degree of vertical impaction than Crouzon syndrome (See *FGFR*-Related Craniosynostosis Syndromes.)
- Prominent eyes with downslanting palpebral fissures
- Relative prognathism with malocclusion

Airway. Multilevel airway obstruction

Limbs/skeleton

- Syndactyly of the hands, including soft tissue and bone
  - The second, third, and fourth fingers are always included in the fusion, while the thumb and fifth digit may or may not be included.
  - Synonychia (fusion of ≥2 nails) of the second through fourth fingers is common. The appearance is sometimes referred to as a "mitten hand."
- Syndactyly of the feet, which may or may not include the great toe
- Tendency toward progressive bony fusion at multiple sites (e.g., progressive craniosynostosis, cervical vertebral fusions, bones of the hands and feet, carpus, and tarsus). Bony fusions (especially of the skull) may also occur after birth.

Establishing the Diagnosis

The diagnosis of Apert syndrome **is established** in a proband with:

- Classic clinical characteristics (multisuture craniosynostosis, midface retrusion, and syndactyly); OR
- Suggestive clinical features AND a heterozygous pathogenic (or likely pathogenic) variant in *FGFR2* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *FGFR2* variant of uncertain significance does not establish or rule out the diagnosis.

When the phenotypic findings suggest the diagnosis of Apert syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Note: All individuals with Apert syndrome have a heterozygous pathogenic variant in *FGFR2*, though clinicians may choose a targeted panel including common pathogenic variants that cause other forms of syndromic craniosynostosis if the diagnosis is unclear or if this approach is the most cost effective.

Single-gene testing. Sequence analysis of *FGFR2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. Typically, exon or whole-gene deletions/duplications are not detected.

- Perform sequence analysis first.
- If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

A craniosynostosis multigene panel that includes *FGFR2* and other genes of interest (see Differential Diagnosis) 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Apert Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FGFR2	Sequence analysis [3]	~99% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Rare [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Park et al [1995], Wilkie et al [1995], Moloney et al [1996], Oldridge et al [1997], Lajeunie et al [1999]
5. Several pathogenic variants are recurrent and commonly seen: p.Ser252Trp (62%-71%), p.Pro253Arg (26%-33%), and p.Ser252Phe (<1%-3%).
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. Oldridge et al [1999], Bochukova et al [2009], Fenwick et al [2011]

Clinical Characteristics

Clinical Description

Apert syndrome shows substantial overlap with the clinical characteristics seen in other *FGFR2*-associated craniosynostosis syndromes (e.g., craniosynostosis, midface retrusion, vertebral fusions). In most individuals, Apert syndrome can be readily distinguished from other syndromic craniosynostosis syndromes (e.g., Crouzon, Pfeiffer, Jackson-Weiss, Beare-Stevenson) at or before birth due to the presence of syndactyly. However, several other important distinguishing features have implications for surveillance and medical management (see Management).

Craniosynostosis is a near-universal finding in individuals with Apert syndrome, though some affected individuals with other typical manifestations (e.g., midface retrusion and syndactyly) without craniosynostosis have been reported. Most infants with Apert syndrome are born with fusion of one or more cranial sutures, though progressive craniosynostosis of other sutures can occur. As bony fusions are typically progressive in Apert syndrome, and most major cranial sutures do not typically fuse until adulthood, it is unknown whether the children reported with Apert syndrome without craniosynostosis at the time of diagnosis would go on to develop craniosynostosis later.

Depending on the involved sutures, most children with Apert syndrome have a large anterior fontanelle, which is displaced anteriorly onto the forehead [Cohen & Kreiborg 1996]. The most commonly involved sutures are the following:

- Coronal (near 100%), though many will have multisuture craniosynostosis or pan synostosis resulting in cloverleaf skull
- Sagittal (~85%)
- Lambdoid (81%)

Midface retrusion. Unlike Crouzon syndrome, in which the midface is normally formed but retruded, the midface in Apert syndrome is underdeveloped as well as retruded. There is a greater degree of vertical impaction leading to a shorter maxillary bone, with greater similarity to Pfeiffer syndrome than to Crouzon syndrome. The underdevelopment of the midface contributes to the development of shallow orbits and downslanting palpebral fissures. Underdeveloped maxillary structures result in malocclusion and the appearance of relative mandibular prognathism [Cohen & Kreiborg 1996].

Palatal abnormalities. Highly arched palate or cleft palate may occur. Cleft palate is frequently present in Apert syndrome (but rarely found in Crouzon syndrome) [Cohen & Kreiborg 1996].

Feeding issues. Feeding problems are common in children with Apert syndrome and have a number of causes. Palatal anomalies can cause difficulty with generating suction and therefore difficulty with intake of sufficient volume.

Narrowing of the choanae or nasal turbinates can cause respiratory distress, which can be mistaken for a primary feeding issue. In this case, the infant will often suck a few times and then unlatch to breathe through an open mouth. Infants who have a primary respiratory cause for their feeding issues generally have difficulty breathing through the nose and have other signs of upper-respiratory obstruction.

Children with Apert syndrome are at risk for gastrointestinal issues (see **Gastrointestinal issues** below) that can cause vomiting but do not typically affect the transfer of milk from the bottle or breast. Many children with Apert syndrome who have feeding difficulties require surgical intervention (e.g., repair of choanal atresia or stenosis, gastrostomy tube).

Clinical feeding evaluation and/or video fluoroscopic swallow study should be performed for all infants to identify aspiration (see Management). If there is aspiration, precautions should be taken (e.g., thickened feeds, limiting oral intake) to prevent aspiration pneumonia, pneumonitis, and chronic lung disease.

Dental abnormalities. Children with Apert syndrome often have dental anomalies that require management by orthodontics and/or oromaxillofacial surgery. Tooth agenesis (typically of maxillary canines) and enamel opacities occur in more than 40% of children with Apert syndrome. Ectopic eruption of maxillary first molars and lateral palatal swellings are also common. Other orthodontic differences include delayed dental eruption, missing teeth, dental crowding, and abnormal occlusal relationships. Abnormalities of primary and adult teeth can be present [Nurko & Quinones 2004, Dalben et al 2006].

Ocular abnormalities. The characteristic appearance of the eyes in Apert syndrome is prominent with downslanting palpebral fissures. The prominence of the eyes is typically due to a combination of bicoronal craniosynostosis and deficient development of the maxilla. Other primary ophthalmologic abnormalities include the following:

- Strabismus (60%)
- Refractive error (34%)
- Anisometropia (19%)

Secondary ophthalmologic findings that may develop over time include exposure keratopathy and corneal scarring (8%) and optic atrophy (8%). These secondary findings may be preventable with aggressive surveillance and treatment of incomplete lid closure and increased intracranial pressure [Khong et al 2006b].

Hearing loss/inner ear anomalies. Hearing loss is common (80%) and is typically conductive, caused by middle ear disease, ossicular abnormalities, and external auditory canal stenosis or atresia [Agochukwu et al 2014].

Abnormalities of the semicircular canals are found in 70% of affected individuals.

Multilevel airway obstruction. Individuals with Apert syndrome may have abnormalities at multiple sites [Cohen & Kreiborg 1992, Cohen & Kreiborg 1996, Wenger et al 2017].

- Narrowing of the nasal passages or choanae can lead to upper-airway obstruction, and may contribute to respiratory distress as well as feeding difficulties.
- Tongue-based airway obstruction may also occur.

  In children with cleft palate, repair of the cleft palate may unmask obstruction at the level of the pharynx and result in worsening of obstructive sleep apnea.
- Tracheal anomalies, including fused rings and tracheal cartilaginous sleeves, have been reported in a number of individuals.
  - Significant variability in severity is seen, ranging from mild respiratory symptoms requiring little intervention to severe obstruction requiring placement of tracheostomy.
  - Some children who require tracheostomy need a ventilator for delivery of positive airway pressure during sleep.

Syndactyly. The hand in Apert syndrome always includes fusion of the middle three digits; the thumb and fifth finger may also be involved. The fingernail for digits 2-4 is typically fused to form a single nail (synonychia). Syndactyly of the toes may involve the lateral three digits, digits 2-5, or all digits. In general, the upper limb is more severely affected than the lower limb. Synonychia has not been reported in the toes [Upton 1991, Cohen & Kreiborg 1995, Wilkie et al 1995].

Other limb anomalies that occur less frequently in individuals with Apert syndrome include the following [Maroteaux & Fonfria 1987, Sidhu & Deshmukh 1988, Gorlin 1989, Lefort et al 1992, Cohen & Kreiborg 1995, Mantilla-Capacho et al 2005]:

- Synostosis of the radius and humerus
- Preaxial and/or postaxial polydactyly of the hands and/or feet
- Broad distal phalanx of the thumb or broad distal hallux

Spinal fusions. Cervical vertebral fusions are found in 68% of individuals with Apert syndrome, most commonly involving C5-C6. Of those with fusions, approximately 50% have a single fusion and 50% have multiple fusions. The prevalence and location of vertebral fusions differs from Crouzon syndrome, in which only 25% have vertebral fusion, most commonly involving C2-C3. If spinal fusions or abnormalities of spinal fusion occur, scoliosis can result [Kreiborg et al 1992]. Other cervical spine anomalies include atlanto-axial subluxation (7%) and C1 spina bifida occulta (7%) [Breik et al 2016].

Progressive synostosis. Progressive fusion of several bones may occur, including bones of the skull, hands, feet, carpus, tarsus, and cervical vertebrae [Schauerte & St-Aubin 1966].

Restriction of movement involving the shoulder due to glenohumeral dysplasia can lead to functional impairment. This restriction tends to be progressive with decrease in forward flexion and abduction of the upper arm limiting the ability of the individual with Apert syndrome to perform "overhead" tasks [McHugh et al 2007, Murnaghan et al 2007].

Children with Apert syndrome may experience progressive deformities of the foot leading to pain and difficulty with gait. Over time the first metatarsal bone becomes relatively short with resultant shift in the weight-bearing function of the first metatarsal to the second metatarsal bone, and the great toes become increasingly short and angulated. Callus formation develops as weight is redistributed laterally leading to pain and limitation of daily activities. Affected individuals experience difficulty finding footwear that fits properly [Calis et al 2016].

Neurologic. Jugular foraminal stenosis is seen in 93% of affected individuals.

Approximately 60% of individuals with Apert syndrome have nonprogressive ventriculomegaly and 6%-13% have hydrocephalus.

- Stable ventriculomegaly does not necessarily require surgical intervention.
- Progressive ventriculomegaly can indicate hydrocephalus, which may require evaluation for endoscopic third ventriculostomy and/or ventriculoperitoneal shunt.

Structural brain malformations in Apert syndrome include the following [Cohen & Kreiborg 1990, Cinalli et al 1995, Renier et al 1996, Quintero-Rivera et al 2006, Tan & Mankad 2018]:

- Abnormalities of the corpus callosum (23%)
- Absent septum pellucidum (17%)
- Chiari I malformation and/or low-lying cerebellar tonsils (17%)

  Note: Only 2% of individuals with Apert syndrome were found to have chronic tonsillar herniation, which is present in 73% of those with Crouzon syndrome.
- Posterior fossa arachnoid cyst (7%)
- Limbic malformations

Neurodevelopment. Most individuals with Apert syndrome have normal intellect or mild intellectual disability, though some individuals have been reported with moderate-to-severe intellectual disability [Renier et al 1996, David et al 2016, Fernandes et al 2016]. Not surprisingly, children with Apert syndrome raised within the family have better cognitive outcomes than children who were institutionalized [Patton et al 1988, Cohen & Kreiborg 1990, Renier et al 1996]. The neurodevelopmental outcomes for children born with Apert syndrome today may be more promising than these earlier reports suggest, as surgical and medical management have become more advanced and children have improved access to early intervention programs.

Factors associated with a higher risk for intellectual disability include the following:

- Delay of first craniectomy until after one year of age
- Presence of structural brain malformations
  - Abnormalities of the septum pellicudum have been shown to be associated with lower IQ.
  - Data regarding the possible impact on IQ of an abnormal callosum and/or corpus callosum are conflicting.

Cardiovascular. Approximately 10% of individuals with Apert syndrome have structural cardiac abnormalities. The most common malformations include ventricular septal defect and overriding aorta; some children with complex congenital heart disease have been reported. Children with complex congenital heart disease are at greater risk for early death compared to children with structurally normal hearts [Cohen & Kreiborg 1993].

Gastrointestinal issues. Feeding difficulties can occur in Apert syndrome for a variety of reasons, and may require placement of a nasogastric or gastric tube.

One of 15 individuals with Apert syndrome had intestinal malrotation in one study, though it was unclear whether the remaining affected individuals had undergone formal radiologic evaluation for malrotation (upper GI); therefore, the true prevalence may be higher than reported [Hibberd et al 2016].

Distal esophageal stenosis has also been reported [Pelz et al 1994].

Other gastrointestinal malformations reported in Apert syndrome include the following:

- Pyloric stenosis
- Esophageal atresia

- Ectopic anus

Genitourinary. Anomalies of the genitourinary tract are identified in 9.6% of children with Apert syndrome, most commonly hydronephrosis or cryptorchidism. One child with Apert syndrome caused by a germline *FGFR2* pathogenic variant had a low-grade papillary urothelial carcinoma of the bladder, but no detected *FGFR3* somatic variants (which can be associated with this type of cancer). As a single case was reported, it is unclear whether this is part of the phenotype of Apert syndrome [Cohen & Kreiborg 1993, Andreou et al 2006].

Skin changes. Hyperhidrosis is a consistent feature of Apert syndrome. Affected adults typically develop oily skin in adolescence and extensive acneiform lesions, including on the face, chest, back, and upper arms. Some affected individuals develop excessive skin wrinkling of the forehead [Cohen & Kreiborg 1995]. Nail dystrophy is also common [Bissacotti Steglich et al 2016].

Adults. A range of educational and employment ascertainment has been described. Adults with Apert syndrome appear to have more challenges with social development and relationships compared to unaffected controls and individuals with Crouzon syndrome [Tovetjärn et al 2012, David et al 2016, Lloyd et al 2016].

Genotype-Phenotype Correlations

Reports regarding genotype-phenotype correlations in Apert syndrome are variable. Some studies suggest no clear correlations [Park et al 1995].

- **Pathogenic p.Pro253Arg variant**
  - Some studies have suggested more significant hand and foot involvement in individuals with this pathogenic variant.
  - One study suggested better postsurgical craniofacial appearance in affected individuals with this variant, but the generalizability of this study is limited due to significant evolution of surgical techniques since the study was published [von Gernet et al 2000].
- **Pathogenic p.Ser252Trp variant.** Cleft palate has been reported to be more common in those with this variant.

No other features of Apert syndrome have been found to vary based on genotype [Slaney et al 1996, Lajeunie et al 1999].

Nomenclature

Apert syndrome may also be referred to as acrocephalysyndactyly type I.

Prevalence

The estimated birth prevalence of Apert syndrome ranges from 1: 80,000 to 1:160,000 live births [Cohen et al 1992, Tolarova et al 1997]. The frequency may be higher among children born to fathers with advanced paternal age, with the greatest number of variants in sperm from fathers older than age 60 years [Glaser et al 2003].

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in ***FGFR2*** are summarized in Tables 2a and 2b. Disorders included in Table 2a have phenotypic features that overlap with Apert syndrome and should be considered in the differential diagnosis.

Table 2a. Allelic Disorders to Consider in the Differential Diagnosis of Apert Syndrome

Allelic Disorder	MOI	Features of Allelic Disorder	
		In common with "classic" Apert syndrome	Not seen in Apert syndrome
FGFR2-related Antley-Bixler syndrome [1]	AD	• Craniosynostosis (coronal & lambdoidal) • Brachyturricephaly w/frontal bossing • Ocular proptosis • Downslanting palpebral fissures • Radiohumeral synostosis	• Depression of nasal bridge • Low-set, protruding ears • Medial bowing of ulnae • Bowing of femurs • Slender hands & feet • Contractures at proximal IP joints • Fractures • Advanced bone age • Congenital heart disease • Renal anomalies • Abnormalities of female genitalia • Signs of congenital adrenal hyperplasia
Beare-Stevenson syndrome [2]	AD	• Craniosynostosis (coronal most common) • Midface hypoplasia	• Natal teeth • Pyloric stenosis • Furrowed palms & soles • Widespread cutis gyrata • Acanthosis nigricans • Skin tags • Prominent umbilicus • Accessory nipples • Bifid scrotum • Prominent labial raphe • Rugated labia majora
Crouzon syndrome [2]	AD	• Craniosynostosis (multisuture, coronal most common) • Brachyturricephaly • Maxillary hypoplasia • Obstructive sleep apnea • Tracheal cartilaginous sleeve • Hypertelorism • Ocular proptosis • Papilledema • Strabismus • Atresia of auditory canals • Conductive hearing loss • Hydrocephalus • Cervical spine fusions	• Chiari 1 malformation more common • Midface retrusion w/less vertical impaction
Jackson-Weiss syndrome [2]	AD	• Craniosynostosis (coronal most common) • Maxillary hypoplasia • Obstructive sleep apnea • Hypertelorism • Ocular proptosis • Strabismus	Radiographic abnormalities of the foot incl: • Fusion of tarsal & metatarsal bones • 2-3 syndactyly • Broad & medially deviated great toes • Short 1st metatarsals • Broad proximal phalanges

Table 2a. continued from previous page.

Allelic Disorder	MOI	Features of Allelic Disorder	
		In common with "classic" Apert syndrome	Not seen in Apert syndrome
Pfeiffer syndrome types 1, 2, & 3 [2]	AD	• Craniosynostosis (multisuture, coronal most common) • Brachyturricephaly • Maxillary hypoplasia • Obstructive sleep apnea • Tracheal cartilaginous sleeve • Hypertelorism • Ocular proptosis • Papilledema • Strabismus • Downslanting palpebral fissures • Atresia of auditory canals • Conductive hearing loss • Hydrocephalus • Cervical spine fusions • Radiohumeral fusions	• Chiari 1 malformation more common • Broad & deviated thumbs & great toes • Brachydactyly
FGFR2-related Saethre-Chotzen syndrome [3]	AD	• Craniosynostosis (unilateral or bilateral coronal) • Brachyturricephaly • Maxillary hypoplasia • Obstructive sleep apnea • High-arched palate • Hypertelorism • Downslanting palpebral fissures • Hearing loss	• Ptosis • Facial asymmetry • Low anterior hairline • Parietal foramina • Characteristic ear (small pinna w/a prominent crus) • Partial 2-3 syndactyly of fingers • Duplicated distal phalanx of hallux

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. Antley-Bixler syndrome is caused by mutation of *FGFR2* or *POR* (Note: *POR*-related Antley-Bixler syndrome is inherited in an autosomal recessive manner.
2. See *FGFR*-Related Craniosynostosis Syndromes.
3. See Saethre-Chotzen Syndrome. Saethre-Chotzen syndrome is typically caused by mutation of *TWIST1*, but a family with phenotypic features of Saethre-Chotzen syndrome and normal *TWIST1* sequence analysis had an *FGFR2* pathogenic variant [Freitas et al 2006].

Table 2b. Other Allelic Disorders (not in the Differential Diagnosis of Apert Syndrome)

Phenotype	References (*GeneReview*, OMIM, or Citation)
Bent-bone dysplasia syndrome	OMIM 614592
Craniofacial-skeletal-dermatologic dysplasia	OMIM 101600
FGFR2-related isolated coronal synostosis	*FGFR*-Related Craniosynostosis Syndromes
Lacrimoauriculodentodigital (LADD) syndrome	OMIM 149730
Syndromic craniosynostosis with elbow contracture	Akai et al 2006
Scaphocephaly, maxillary retrusion, and intellectual disability	OMIM 609579

Sporadic tumors (including gastric cancer) occurring as single tumors in the absence of any other findings of Apert syndrome frequently harbor somatic variants in *FGFR2* that are **not** present in the germline. In these circumstances predisposition to these tumors is not heritable. For more details, see Cancer and Benign Tumors.

Differential Diagnosis

Most children with multisuture synostosis will have a syndromic form of craniosynostosis. The presence of specific craniofacial characteristics and hand and foot anomalies allow for the clinical diagnosis of Apert syndrome in most cases. Establishing an accurate diagnosis has important implications for screening, surveillance, management, and counseling (see Management and Genetic Counseling).

Select syndromes to consider in the differential diagnosis of Apert syndrome include the allelic disorders listed in Table 2a (*FGFR2*-related Antley-Bixler syndrome, Beare-Stevenson syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Pfeiffer syndrome types 1, 2, and 3, *FGFR2*-related Saethre-Chotzen syndrome) and the select syndromes listed in Table 3.

Table 3. Nonallelic Craniosynostosis Syndromes to Consider in the Differential Diagnosis of Apert Syndrome

Gene	Disorder	MOI	Features of the Differential Diagnosis Disorder	
			In common with "classic" Apert syndrome	Not seen in Apert syndrome
POR	*POR*-related Antley-Bixler syndrome [1]	AR	See Table 2a.	See Table 2a.
RAB23	Carpenter syndrome	AD	• Craniosynostosis (multisuture, coronal most common) • Brachyturricephaly • Maxillary hypoplasia • Obstructive sleep apnea • Hypertelorism • Ocular proptosis	Brachydactyly w/o syndactyly
FGFR3	Muenke syndrome	AD	• Craniosynostosis (unilateral or bilateral coronal) • Mild maxillary hypoplasia • Downslanting palpebral fissures • Cervical spine fusions	• Sensorineural hearing loss • Brachydactyly • Carpal-tarsal fusion • Carpal bone malsegregation • Coned epiphyses
FGFR1	*FGFR1*-related Pfeiffer syndrome types 1, 2, & 3 [2]	AD	See Table 2a.	See Table 2a.
TWIST1	*TWIST1*-related Saethre-Chotzen syndrome [3]	AD	See Table 2a.	See Table 2a.

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

1. Antley-Bixler syndrome is caused by mutation of *FGFR2* or *POR*.

2. Pfeiffer syndrome is caused by mutation of *FGFR1* or *FGFR2*. See *FGFR*-Related Craniosynostosis Syndromes.

3. Saethre-Chotzen syndrome is typically caused by mutation of *TWIST1*, but a family with phenotypic features of Saethre-Chotzen syndrome and normal *TWIST1* sequence analysis had an *FGFR2* pathogenic variant [Freitas et al 2006].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Apert syndrome, the evaluations summarized in Table 4 (if not already performed) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Apert Syndrome

System/ Concern	Evaluation	Comment
Craniofacial	Physical exam to identify cleft palate, ear anomalies, face shape, fontanelles, suture ridging, & skull base symmetry	Assessing degree of maxillary hypoplasia is important for determining risk for airway compromise.
Eyes	Consultation w/pediatric ophthalmologist [1]	Incl assessment of eye surfaces, eye alignment, & optic nerves
Ears	Ear-specific hearing eval	
Respiratory	Assess for airway symptoms (snoring, stridor, apnea, respiratory distress).	
	Overnight polysomnography (sleep study)	To identify & quantify degree of sleep apnea [2]
	Consider consultation w/otolaryngologist & sleep medicine	Airway endoscopy (flexible bedside endoscopy & diagnostic laryngoscopy & bronchoscopy) may help identify types & degree of airway narrowing. [3]
Cardiovascular	Cardiac assessment	Echocardiogram if a murmur is present or if clinical cardiac concerns
Gastrointestinal	Upper GI w/small bowel follow-through if symptomatic or during preoperative eval for gastrostomy tube	To evaluate for intestinal malrotation
Genitourinary	Assessment for cryptorchidism in males	Referral to urologist
	Renal ultrasound	To evaluate for hydronephrosis
Musculoskeletal	CT scan of head/skull/sutures	CT w/3D reconstruction will delineate degree of suture involvement & help w/preoperative planning.
	Cervical spine imaging to evaluate for vertebral fusions & instability	CT of cervical spine before cranial surgery; or perform radiograph after age 2 yrs (when vertebrae are ossified)
	Hand radiographs to evaluate extent of syndactyly, which commonly includes bony fusion, or symphalangism	Consultation w/hand surgeon
Neurologic	CT scan or MRI of the head to evaluate for hydrocephalus & CNS anomalies	If concern for hydrocephalus or Chiari malformation, consider brain MRI.
Other	Assessment for developmental disabilities	Consider referral to a neurodevelopmental specialist / early intervention services
	Consultation w/clinical geneticist & genetic counselor	To incl recurrence risk counseling

CNS = central nervous system; CT = computed tomography; GI = gastrointestinal; MRI = magnetic resonance imaging

1. Early detection and management of amblyopia, encouraging timely decompressive surgery before the presence of optic nerve atrophy, and protection of the cornea are the management goals for ophthalmologists [Khong et al 2006a].

2. Inverso et al [2016]

3. Doerga et al [2016]

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Apert Syndrome

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]

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Midface retrusion	Jaw surgery to advance the midface	Typically in childhood or adolescence [6, 7]
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 evaluate swallowing safety & support eating by mouth.	
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 orofacial 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.
Hearing loss	Placement of tympanostomy tubes	If chronic middle ear effusions are present
	Hearing aids, bone conduction sound processors, tympanoplasties, & aural atresia/ stenosis repair	Optimizing hearing will facilitate language & communication development.
Airway obstruction	Awareness of potential airway compromise & proactive airway mgmt are crucial in infants & children.	Specific airway mgmt in Apert syndrome will depend on level & severity of obstruction.
	Temporizing measures to bypass airway obstruction: • Placement of nasal stents • Endotracheal intubation • Tracheotomy	Infants & children requiring tracheotomy may also need positive pressure ventilation to normalize gas exchange & achieve normal sleep & growth. [9]
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 because pressure on midface exacerbates midfacial retrusion.
	Supplemental oxygen via nasal cannula is sometimes beneficial.	Reducing sleep apnea & improving sleep quality can improve learning, cognition, & behavior.
Congenital heart defects	Standard treatment per cardiologist	
Malrotation	Standard treatment per surgeon	
Cryptorchidism in males or hydronephrosis	Standard treatment per urologist	
Syndactyly	Type & timing of surgeries depends on presence of thumb syndactyly & extent of soft tissue deficiency.	A common goal: improve hand & foot function w/fewest surgeries
	Treatment can be separated into early phase (syndactyly releases) & late phases (functional osteotomies). [10, 11]	Most persons require multiple procedures & revisions throughout childhood. [12]
Scoliosis	Standard treatment per orthopedist	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Speech abnormalities [8]	Speech evaluation by speech-language pathologist w/craniofacial expertise to guide speech therapy recommendations	
Developmental delay	Early intervention services	Consider consultation w/developmental pediatrician or neurodevelopmental specialist.
Acne	Oral isotretinoin may be considered for those w/refractory acne not responsive to standard therapies. [13]	Oral isotretinoin is a known human teratogen & should be not prescribed to females of childbearing age unless 2 independent forms of birth control are instituted & monthly pregnancy tests performed.
Emotional & behavioral adjustment	Psychosocial assessments & mental health support throughout childhood [14]	Recognize & address potential bullying/ teasing by peers.

1. Cranioplasty involves release of fused sutures and repositioning and reconstruction of the calvaria, in order to prevent increased ICP and reduce progressive abnormal craniofacial development.
2. Several techniques including endoscopic strip craniectomy, advancement through posterior distraction, and traditional cranioplasty are in current use.
3. Early surgery may be performed to reduce intracranial pressure; however, young infants with Apert syndrome may have minimal reserve. 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 Apert and bicoronal craniosynostosis will benefit from a front-orbital advancement.
5. The goals of craniofacial surgery are to provide adequate intracranial volume to allow brain development and to improve skull shape. The timing and sequence of surgical interventions are dependent on the patient'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. Articulation, resonance, language development, voice, feeding, and swallowing may be affected in individuals with Apert syndrome.
9. Serious caution must be taken in the placement and care of tracheostomies in patients with tracheal cartilaginous sleeve malformation because of abnormal tissue healing and granulation tissue formation [Wenger et al 2017].
10. Fearon [2003]
11. Recent studies describe novel techniques to improve aesthetic outcomes in children with complex syndactylies [Lohmeyer et al 2016].
12. Pettitt et al [2017]
13. 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].
14. 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].

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross and fine motor dysfunction. Children with Apert syndrome have difficulty with the use of their hands for functions such as feeding, grooming, dressing, and writing. The goal of hand surgeries is to separate fingers to restore capacity for function to the hands. Most children with Apert will require therapy to maximize use of their hands secondary to polysyndactyly and fusions. Most individuals will have multiple hand surgeries, and physical and occupational therapy before and after surgery to maximize function. There is regional variation in whether these services are provided by physical therapy, occupational therapy, or a combination of the two.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding because of poor oral motor control. In Apert syndrome, feeding difficulties often signal worsening upper-airway obstruction, so the therapist should be in communication with the craniofacial team to ensure that surgical intervention is not needed.

Adults

Comprehensive care provided by a specialized craniofacial center that includes psychosocial support and holistic transition (to adult care) planning may improve quality of life for adults with Apert syndrome.

Prevention of Secondary Complications

Table 6. Prevention of Secondary Manifestations in Individuals with Apert Syndrome

Manifestation/Concern	Prevention	Considerations/Other
Papilledema / Cognitive impairment	Timely surgical treatment of craniosynostosis	
Exposure keratopathy & corneal scarring due to ocular proptosis	Ocular lubricants	Monitoring of eye surfaces, eye alignment, & vision recommended to prevent & ↓ visual loss
Perioperative respiratory complications [1]	Anesthesia eval before any surgical intervention for those w/potential airway challenges may improve communication & outcomes.	Risks related to anesthesia are higher in those w/Apert syndrome. [2]

Table 6. continued from previous page.

Manifestation/Concern	Prevention	Considerations/Other
Aspiration pneumonia w/ subsequent chronic lung disease	Aspiration precautions (e.g., thickened feeds, limiting oral intake)	Clinical feeding eval &/or video fluoroscopic swallowing study may help determine aspiration risk.
Spinal cord injury & neurologic sequelae	• Vigilance regarding spine precautions • Consultation w/spine surgeon will guide precautions & positioning prior to surgery & anesthesia.	In those w/cervical spine anomalies

1. Most commonly upper-airway obstruction (6.1%) [Barnett et al 2011]
2. While upper-airway obstruction is the most common, lower respiratory-tract complications during anesthesia have also been reported [Elwood et al 2001].

Surveillance

A craniofacial team made up of the appropriate specialties allows for proper planning and coordination so that the affected individual may receive the best possible care [McCarthy et al 2012].

Ideally, the composition of the multidisciplinary team caring for a child with Apert syndrome should include the following specialists:

- Audiologist
- Dentist
- Dermatologist
- Feeding specialist
- Geneticist
- Neurodevelopmental and behavioral pediatrician
- Neurosurgeon
- Nurse
- Nutritionist
- Ophthalmologist
- Oral surgeon
- Orthodontist
- Orthopedist (hand and foot surgery)
- Otolaryngologist
- Pediatrician
- Plastic surgeon
- Psychologist
- Pulmonologist / sleep medicine
- Social worker
- Speech pathologist
- Spine surgeon

Table 7. Recommended Surveillance for Individuals with Apert Syndrome

System/Concern	Evaluation	Frequency
Oropharynx	Assessment for velopharyngeal insufficiency [1, 2]	After emergence of language
	Speech assessment to monitor for speech disorders	At least annually
Dental	Assessments w/primary dentist to ↓ caries & support dental health [3]	Every 6 mos

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Eyes	Ophthalmologic eval to incl vision, eye alignment, & dilated fundoscopy to assess optic nerves [4]	Annually
Ears	Audiologic & otologic assessements	At least annually
Musculoskeletal	Monitor for development of scoliosis by clinical exam w/ surveillance spine radiographs if recommended by spine surgeon.	Annually in childhood & adolescence
Neurologic	Measurements of head circumference (& fontanelle size, if applicable) to monitor for progressive hydrocephalus	At each appointment in infancy & early childhood
	Assessments for ↑intracranial pressure [5, 6]	
	Eval by craniofacial team	Regularly, esp in infancy, childhood, & adolescence
Development/ Cognition	Assessment of developmental progress	At each visit

1. For those with cleft palate
2. Orthognathic and airway procedures may also alter velopharyngeal function.
3. Surveillance by an orthodontist with craniofacial expertise beginning in mixed dentition will help guide orthodontic and orthognathic interventions.
4. Papilledema in individuals with multisuture craniosynostosis can occur before and after cranial decompression [Bannink et al 2008].
5. The type of surveillance needed depends on the types of surgery that the child has had and will be determined by the neurosurgeon and craniofacial team.
6. The craniofacial team should be contacted urgently if there are symptoms that suggest increased pressure such as unexplained persistent vomiting, headaches, or changes in head circumference.

Agents/Circumstances to Avoid

Contact sports and activities that involve neck hyperflexion or extension should be avoided, unless the individual has had the cervical spine assessed and cleared.

Avoid factors that potentiate hearing loss (ototoxic medications, overly loud stimuli).

Use of CPAP/BiPAP for long-term treatment of sleep apnea should be avoided when possible because pressure on the midface will exacerbate midfacial retrusion.

Evaluation of Relatives at Risk

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

Pregnancy Management

No published studies address management of pregnancy in women with Apert syndrome.

Affected pregnant women should be monitored carefully for signs and symptoms of worsening obstructive sleep apnea.

A pregnant woman with Apert syndrome should have a careful anesthesia evaluation prior to initiation of labor to determine whether multilevel airway anomalies or vertebral anomalies would result in additional risk with certain types of anesthesia.

- If an obstetric emergency necessitates use of general anesthesia, fiberoptic intubation could be required.
- If this need were identified prior to delivery, the delivery location and timing could be chosen to ensure that adequate personnel were present to perform fiberoptic intubation, if needed.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register 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.

Genetic Counseling

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

Apert syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with Apert syndrome have an affected parent.
- Most individuals diagnosed with Apert syndrome have the disorder as the result of a *de novo FGFR2* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown. Advanced paternal age has been shown clinically to be associated with *de novo* pathogenic variants for 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].
- Molecular genetic testing can be performed on the parents of a proband with an apparent *de novo* pathogenic variant; however; such testing is unlikely to provide additional information as the genetic status of the parents can be inferred based on their clinical status (Apert syndrome is 100% penetrant and therefore a heterozygous parent will be clinically affected).
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is germline mosaicism in a parent. Parental germline mosaicism has been reported in a family with affected sisters born to unaffected parents [Allanson 1986].

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

- If a parent of the proband is affected, the risk to sibs is 50%.
- If the parents are unaffected and/or the proband has a known *FGFR2* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Allanson 1986].

Offspring of a proband. Each child of an individual with Apert syndrome has a 50% chance of inheriting the *FGFR2* 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 *FGFR2* pathogenic variant, the parent's other family members may be at risk.

Related Genetic Counseling Issues

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.

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

Once the *FGFR2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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
- **Children's Craniofacial Association (CCA)**
  13140 Coit Road
  Suite 517
  Dallas TX 75240
  Phone: 800-535-3643 (toll-free); 214-570-9099
  Fax: 214-570-8811
  Email: contactCCA@ccakids.com
  A Guide to Understanding Apert Syndrome
- **National Library of Medicine Genetics Home Reference**
  Apert syndrome

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Apert Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FGFR2	10q26.13	Fibroblast growth factor receptor 2	FGFR2 @ LOVD	FGFR2	FGFR2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Apert Syndrome (View All in OMIM)

101200	APERT SYNDROME
176943	FIBROBLAST GROWTH FACTOR RECEPTOR 2; FGFR2

Molecular Pathogenesis

FGFR2 belongs to a complex system of intracellular signaling consisting of multiple fibroblast growth factors (FGFs) and their receptors FGFRs. This signaling network functions in the control of cell proliferation, differentiation, migration, and death in many different contexts such as embryonic development, angiogenesis, immunity, and cancer. Diseases result from loss-of-function, gain-of-function, postzygotic mosaic, and/or somatic alterations in components of this network. For an excellent overview of this signaling network, along with effects of germline and somatic alterations in FGFs and FGFRs that result in human disease, see Katoh [2016] and references therein. Additionally Azoury et al [2017] focuses on *FGFR*-related craniosynostosis.

Gene structure. The transcript NM_000141.4 has 18 exons, with exon 1 being noncoding. The coding sequence, 648-3113 nt, encodes a signal peptide (648-710 nt) and the mature protein (711-3110 nt). This transcript may be referred to as transcript variant 1. Multiple alternatively spliced transcript variants encoding different isoforms are described. For a detailed summary of gene, transcripts, and protein isoforms, see Table A, **Gene**.

Pathogenic variants. Apert syndrome results from a gain of function of FGFR2, and as expected the range of pathogenic variants is limited. The recurrent and common variants p.Ser252Trp, p.Pro253Arg, and p.Ser252Phe cause the great majority of Apert syndrome (see Table 1, footnote 5). The corresponding nucleotide changes are in 5' end of exon 7. Novel variants are also known, including a splicing variant in intron 8 [Torres et al 2015] and gross deletions that alter the Ig-like domain structure (see **Normal gene product**). The latter include a 1.9-kb deletion that includes the extracellular IG-like domain IIIc (exon 8) and a 1.3-kb deletion (exon 9) that creates a chimeric IIIb/IIIc domain [Bochukova et al 2009, Fenwick et al 2011]. Three gross *de novo* insertions of *Alu* elements in or near exon 9, which encodes domain IIIc, are also described [Oldridge et al 1999, Bochukova et al 2009]. These novel variants are thought to result in exon skipping or other possible dysregulation that ultimately results in a gain of function.

Note that some literature describing pathogenic variants confuses the terminology of exon and domain. Alterations in exons 8 and 9, which encode IG-like domain IIIb and IIIc, respectively, may be referred to as alterations in exon IIIb and exon IIIc.

Table 8. *FGFR2* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.755_756delCGinsTT	p.Ser252Phe [1]	NM_000141.4 NP_000132.3
c.755C>G [2]	p.Ser252Trp [1, 3]	
c.756_758delGCCinsCTT	p.Pro253Phe	
c.758C>G [4]	p.Pro253Arg [1, 3]	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Table 1, footnote 5.
2. Originally published as C934G [Wilkie et al 1995]
3. See Genotype-Phenotype Correlations.
4. Originally published as C937G [Wilkie et al 1995]

Normal gene product. Transcript NM_000141.4 encodes FGFR2 isoform 1 NP_000132.3 (also referred to as isoform BEK) of 821 amino acid residues.

A signal peptide, residues 1-21, is cleaved in post-translational processing to give the mature peptide, residues 22-821, which consists of an extracellular region composed of three immunoglobulin-like domains, a single hydrophobic membrane-spanning segment, and a cytoplasmic tyrosine kinase domain. Residues Ser252 and Pro253, the sites of recurrent pathogenic variants, are located in the linker between the second and third immunoglobulin-like domains.

Abnormal gene product. The gain-of-function *FGFR2* variants are thought to reduce dissociation of ligand leading to enhanced signaling.

Cancer and Benign Tumors

Sporadic tumors occurring as single tumors in the absence of any other clinical findings of Apert syndrome frequently harbor somatic variants in *FGFR2* that are not present in the germline. In these circumstances predisposition to these tumors is not heritable.

Somatic loss-of-function, gain-of-function, and gene fusions involving *FGFR2* are reported in diverse cancers such melanoma, breast, gastric, endometrial, lung, and cholangiocarcinoma. For an excellent overview of FGF signaling network, along with effects of germline and somatic alterations in human disease, see Katoh [2016] and references therein.

Chapter Notes

Acknowledgments

The authors would like to acknowledge Dr Carrie Heike for her critical review of this *GeneReview*.

Revision History

- 30 May 2019 (ma) Review posted live
- 31 December 2017 (tw) Original submission

References

Literature Cited

Agochukwu NB, Solomon BD, Muenke M. Hearing loss in syndromic craniosynostoses: otologic manifestations and clinical findings. Int J Pediatr Otorhinolaryngol. 2014;78:2037–47. PubMed PMID: 25441602.

Akai T, Yamamoto K, Iizuka H, Kawakami S, Yoshida J, Kakinuma H, Yaguchi Y, Ozawa T. Syndromic craniosynostosis with elbow joint contracture. Pediatr Neurosurg. 2006;42:108–12. PubMed PMID: 16465081.

Allanson JE. Germinal mosaicism in Apert syndrome. Clin Genet. 1986;29:429–33. PubMed PMID: 3742849.

Andreou A, Lamy A, Layet V, Cailliez D, Gobet F, Pfister C, Menard M, Frebourg T. Early-onset low-grade papillary carcinoma of the bladder associated with Apert syndrome and a germline FGFR2 mutation (Pro253Arg). Am J Med Genet A. 2006;140:2245–7. PubMed PMID: 16969861.

Azoury SC, Reddy S, Shukla V, Deng CS. Fibroblast growth factor receptor 2 (FGFR2) mutation related syndromic craniosynostosis. Int J Biol Sci. 2017;13:1479–88. PubMed PMID: 29230096.

Bannink N, Joosten KF, van Veelen ML, Bartels MC, Tasker RC, van Adrichem LN, van der Meulen JJ, Vaandrager JM, de Jong TH, Mathijssen IM. Papilledema in patients with Apert, Crouzon, and Pfeiffer syndrome: prevalence, efficacy of treatment, and risk factors. J Craniofac Surg. 2008;19:121–7. PubMed PMID: 18216676.

Barnett S, Moloney C, Bingham R. Perioperative complications in children with Apert syndrome: a review of 509 anesthetics. Paediatr Anaesth. 2011;21:72–7. PubMed PMID: 21073626.

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.

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.

Calis M, Oznur A, Ekin O, Vargel I. Correction of brachymetatarsia and medial angulation of the great toe of Apert foot by distraction osteogenesis: a review of 7 years of experience. J Pediatr Orthop. 2016;36:582–8. PubMed PMID: 25929771.

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 U S A. 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.

Cohen MM, Kreiborg S. The central nervous system in the Apert syndrome. Am J Med Genet. 1990;35:36–45. PubMed PMID: 2405668.

Cohen MM Jr, Kreiborg S. A clinical study of the craniofacial features in Apert syndrome. Int J Oral Maxillofac Surg. 1996;25:45–53. PubMed PMID: 8833300.

Cohen MM, Kreiborg S. Cutaneous manifestations of Apert syndrome. Am J Med Genet. 1995;58:94–6. PubMed PMID: 7573165.

Cohen MM Jr, Kreiborg S. Upper and lower airway compromise in the Apert syndrome. Am J Med Genet. 1992;44:90–3. PubMed PMID: 1519659.

Cohen MM, Kreiborg S. Visceral anomalies in the Apert syndrome. Am J Med Genet. 1993;45:758–60. PubMed PMID: 8456856.

Cohen MM Jr, Kreiborg S, Lammer EJ, Cordero JF, Mastroiacovo P, Erickson JD, Roeper P, Martínez-Frías ML. Birth prevalence study of the Apert syndrome. Am J Med Genet. 1992;42:655–9. PubMed PMID: 1303629.

Dalben GS, et al. Oral findings in patients with Apert syndrome. J Appl Oral Sci. 2006;14:465–9. PubMed PMID: 19089249.

David DJ, Anderson P, Flapper W, Syme-Grant J, Santoreneos S, Moore M. Apert syndrome: outcomes from the Australian Craniofacial Unit's Birth to Maturity Management Protocol. J Craniofac Surg. 2016;27:1125–34. PubMed PMID: 27380568.

Doerga PN, Spruijt B, Mathijssen IM, Wolvius EB, Joosten KF, van der Schroeff MP. Upper airway endoscopy to optimize obstructive sleep apnea treatment in Apert and Crouzon syndromes. J Craniomaxillofac Surg. 2016;44:191–6. PubMed PMID: 26712482.

Elwood T, Sarathy PV, Geiduschek JM, Ulma GA, Karl HW. Respiratory complications during anaesthesia in Apert syndrome. Paediatr.Anaesth. 2001;11:701–3. PubMed PMID: 11696147.

Fearon JA. Treatment of the hands and feet in Apert syndrome: an evolution in management. Plast Reconstr Surg. 2003;112:1–12. PubMed PMID: 12832871.

Fenwick AL, Bowdin SC, Klatt RE, Wilkie AO. 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.

Fernandes MB, Maximino LP, Perosa GB, Abramides DV, Passos-Bueno MR, Yacubian-Fernandes A. Apert and Crouzon syndromes--cognitive development, brain abnormalities, and molecular aspects. Am J Med Genet A. 2016;170:1532–7. PubMed PMID: 27028366.

Freitas EC, Nascimento SR, de Mello MP, Gil-da-Silva-Lopes VL. Q289P mutation in FGFR2 gene causes Saethre-Chotzen syndrome: some considerations about familial heterogeneity. Cleft Palate Craniofac J. 2006;43:142–7. PubMed PMID: 16526917.

Glaser RL, Broman KW, Schulman RL, Eskenazi B, Wyrobek AJ, Jabs EW. The paternal-age effect in Apert syndrome is due, in part, to the increased frequency of mutations in sperm. Am J Hum Genet. 2003;73:939–47. PubMed PMID: 12900791.

Goriely A, McVean GA, Röjmyr 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.

Gorlin RJ. Apert syndrome with polysyndactyly of the feet. Am J Med Genet. 1989;32:557. PubMed PMID: 2774006.

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. 2016;170:3215–21. PubMed PMID: 27481450.

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.

Inverso G, Brustowicz KA, Katz E, Padwa BL. The prevalence of obstructive sleep apnea in symptomatic patients with syndromic craniosynostosis. Int J Oral Maxillofac Surg. 2016;45:167–9. PubMed PMID: 26602951.

Katoh M. Therapeutics targeting FGF signaling network in human diseases. Trends Pharmacol Sci. 2016;37:1081–96. PubMed PMID: 27992319.

Khong JJ, Anderson P, Gray TL, Hammerton M, Selva D, David D. Ophthalmic findings in Apert syndrome prior to craniofacial surgery. Am J Ophthal. 2006a;142:328–30. PubMed PMID: 16876521.

Khong JJ, Anderson P, Gray TL, Hammerton M, Selva D, David D. Ophthalmic findings in Apert's syndrome after craniofacial surgery: twenty-nine years' experience. Ophthalmology. 2006b;113:347–52. PubMed PMID: 16458095.

Kreiborg S, Barr M, Cohen MM. Cervical spine in the Apert syndrome. Am J Med Genet. 1992;43:704–8. PubMed PMID: 1621762.

Lajeunie E, Cameron R, El Ghouzzi V, de Parseval N, Journeau P, Gonzales M, Delezoide AL, Bonaventure J, Le Merrer M, Renier D. Clinical variability in patients with Apert's syndrome. J Neurosurg. 1999;90:443–7. PubMed PMID: 10067911.

Lefort G, Sarda P, Humeau C, Rieu D. Apert syndrome with partial preaxial polydactyly. Genet Counsel. 1992;3:107–9. PubMed PMID: 1642807.

Lloyd MS, Venugopal A, Horton J, Rodrigues D, Nishikawa H, White N, Solanki G, Noons P, Evans M, Dover S. The quality of life in adult patients with syndromic craniosynostosis from their perspective. J Craniofac Surg. 2016;27:1510–4. PubMed PMID: 27438436.

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.

Maroteaux P, Fonfria MC. Apparent Apert syndrome with polydactyly: rare pleiotropic manifestation or new syndrome? Am J Med Genet. 1987;28:153–8. PubMed PMID: 3674108.

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.

McHugh T, Wyers M, King E. MRI characterization of the glenohumeral joint in Apert syndrome. Pediatr Radiol. 2007;37:596–9. PubMed PMID: 17453189.

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.

Moloney DM, Slaney SF, Oldridge M, Wall SA, Sahlin P, Stenman G, Wilkie AOM. Exclusive paternal origin of new mutations in Apert syndrome. Nature Genet. 1996;13:48–53. PubMed PMID: 8673103.

Murnaghan LM, Thurgur CH, Forster BB, Sawatzky BJ, Hawkins R, Tredwell SJ. A clinicoradiologic study of the shoulder in Apert syndrome. J Pediatr Orthop. 2007;27:838–43. PubMed PMID: 17878796.

Nurko C, Quinones R. Dental and orthodontic management of patients with Apert and Crouzon syndromes. Oral Maxillofac Surg Clin North Am. 2004;16:541–53. PubMed PMID: 18088753.

Oldridge M, Lunt PW, Zackai EH, McDonald-McGinn DM, Muenke M, Moloney DM, Twigg SRF, Heath JK, Howard TD, Hoganson G, Gagnon DM, Jabs EW, Wilkie AOM. Genotype-phenotype correlation for nucleotide substitutions in the IgII-IgIII linker of FGFR2. Hum Mol Genet. 1997;6:137–43. PubMed PMID: 9002682.

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.

Park WJ, Theda C, Maestri NE, Meyers GA, Fryburg JS, Dufresne C, Cohen MM, Jabs EW. Analysis of phenotypic features and FGFR2 mutations in Apert syndrome. Am J Hum Genet. 1995;57:321–8. PubMed PMID: 7668257.

Patton MA, Goodship J, Hayward R, Lansdown R. Intellectual development in Apert's syndrome: a long term follow up of 29 patients. J Med Genet. 1988;25:164–7. PubMed PMID: 3351902.

Pelz L, Unger K, Radke M. Esophageal stenosis in acrocephalosyndactyly type I. Am J Med Genet. 1994;53:91. PubMed PMID: 7802047.

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.

Quintero-Rivera F, Robson CD, Reiss RE, Levine D, Benson CB, Mulliken JB, Kimonis VE. Intracranial anomalies detected by imaging studies in 30 patients with Apert syndrome. Am J Med Genet. 2006;140:1337–8. PubMed PMID: 16691624.

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.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Schauerte EW, St-Aubin PM. Progressive synosteosis in Apert's syndrome (acrocephalosyndactyly): with a description of roentgenographic changes in the feet. Am J Roentgenol Radium Ther Nucl Med. 1966;97:67–73.

Sidhu SS, Deshmukh R. Recessive inheritance of apparent Apert syndrome with polysyndactyly? Am J Med Genet. 1988;31:179–80. PubMed PMID: 2851938.

Slaney SF, Oldridge M, Hurst JA, Morriss-Kay GM, Hall CM, Poole MD, Wilkie AOM. Differential effects of FGFR2 mutations on syndactyly and cleft palate in Apert syndrome. Am J Hum Genet. 1996;58:923–32. PubMed PMID: 8651276.

Tan AP, Mankad K. Apert syndrome: magnetic resonance imaging (MRI) of associated intracranial anomalies. Childs Nerv Syst. 2018;34:205–16. PubMed PMID: 29198073.

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.

Tolarova MM, Harris JA, Ordway DE, Vargervik K. Birth prevalence, mutation rate, sex ratio, parents' age, and ethnicity in Apert syndrome. Am J Med Genet. 1997;72:394–8. PubMed PMID: 9375719.

Torres L, Hernández G, Barrera A, Ospina S, Prada R. Molecular analysis of exons 8, 9 and 10 of the fibroblast growth factor receptor 2 (FGFR2) gene in two families with index cases of Apert syndrome. Colomb Med (Cali). 2015;46:150–3. PubMed PMID: 26600631.

Tovetjärn R, Tarnow P, Maltese G, Fischer S, Sahlin PE, Kölby L. Children with Apert syndrome as adults: a follow-up study of 28 Scandinavian patients. Plast Reconstr Surg. 2012;130:572e–6e.

Upton J. Classification and pathologic anatomy of limb anomalies. Clin Plast Surg. 1991;18:321–55. PubMed PMID: 2065493.

von Gernet S, Golla A, Ehrenfels Y, Schuffenhauer S, Fairley JD. Genotype-phenotype analysis in Apert syndrome suggests opposite effects of the two recurrent mutations on syndactyly and outcome of craniofacial surgery. Clin Genet. 2000;57:137–9. PubMed PMID: 10735635.

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.

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.

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.

License