GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

FGFR-Related Craniosynostosis Syndromes

[*Acrocephalosyndactyly. Includes: FGFR1-Related Craniosynostosis (includes: Pfeiffer Syndrome Types 1, 2, and 3), FGFR2-Related Craniosynostosis (includes: Apert Syndrome, Beare-Stevenson Syndrome, Crouzon Syndrome, FGFR2-Related Isolated Coronal Synostosis, Jackson-Weiss Syndrome, Pfeiffer Syndrome Types 1, 2, and 3), FGFR3-Related Craniosynostosis (Crouzon Syndrome with Acanthosis Nigricans, FGFR3-Related Isolated Coronal Synostosis [includes: Muenke Syndrome])*]

Nathaniel H Robin, MD
Departments of Genetics and Pediatrics
University of Alabama at Birmingham
Birmingham, AL
nrobin@uab.edu

Marni J Falk, MD
Division of Human Genetics
Children's Hospital of Philadelphia
Philadelphia, PA
falkm@email.chop.edu

Chad R Haldeman-Englert, MD
Division of Human Genetics
Children's Hospital of Philadelphia
Philadelphia, PA
haldemanenglert@email.chop.edu

Initial Posting: October 20, 1998.
Last Update: September 27, 2007.

Summary

Disease characteristics. The eight disorders comprising the FGFR-related craniosynostosis spectrum are Pfeiffer syndrome, Apert syndrome, Crouzon syndrome, Beare-Stevenson syndrome, *FGFR2*-related isolated coronal synostosis, Jackson-Weiss syndrome, Crouzon syndrome with acanthosis nigricans (AN), and Muenke syndrome (isolated coronal synostosis caused by the p.Pro250Arg mutation in *FGFR3*). Muenke syndrome and *FGFR2*-related isolated coronal synostosis are characterized only by uni- or bicoronal craniosynostosis; the remainder are characterized by bicoronal craniosynostosis or cloverleaf skull, distinctive facial features, and variable hand and foot findings.

Diagnosis/testing. The diagnosis of Muenke syndrome is based on identification of the p.Pro250Arg mutation in *FGFR3*; the diagnosis of *FGFR2*-related isolated coronal synostosis is based on identification of a disease-causing mutation in the *FGFR2* gene. The diagnosis of the other six FGFR-related craniosynostosis syndromes is based on clinical findings; molecular genetic testing of the *FGFR1*, *FGFR2*, and *FGFR3* genes may be helpful in establishing the specific diagnosis in questionable cases.

Management. *Treatment of manifestations:* management by a multidisciplinary craniofacial clinic affiliated with a major pediatric medical center when possible; syndromic craniosynostosis usually requires a series of staged surgical procedures (craniotomy and fronto-orbital advancement) tailored to individual needs; for syndromic craniosynostosis, the first surgery is often as early as age three months, for nonsyndromic craniosynostosis the first surgery is often between ages six months and one year; congenital spine anomalies need

immediate attention; surgical correction of limb defects is usually not possible owing to the nature of the skeletal anomalies. *Prevention of secondary complications:* Early treatment of craniofacial anomalies may reduce the risk for secondary complications such as hydrocephalus and cognitive impairment; ophthalmologic lubrication to prevent exposure keratopathy in those with severe proptosis. *Surveillance:* for hydrocephalus in those at increased risk. *Testing of relatives at risk:* evaluation of at-risk relatives clinically and radiographically or with molecular genetic testing if the disease-causing mutation in the family is known, so that mildly affected relatives can benefit from early intervention.

Genetic counseling. The FGFR-related craniosynostosis syndromes are inherited in an autosomal dominant manner. Affected individuals have a 50% chance of passing the disease-causing mutation to each child. Prenatal testing for pregnancies at increased risk is available if the disease-causing mutation has been identified in the family; however, its use is limited by poor predictive value.

Diagnosis

Clinical Diagnosis

The diagnosis of six of the eight "FGFR-related craniosynostosis" disorders is based primarily on the clinical findings of bilateral coronal craniosynostosis or cloverleaf skull, characteristic facial features, and variable hand and foot findings; molecular genetic testing for heterozygous mutations in *FGFR1*, *FGFR2*, or *FGFR3* may be useful adjuncts in questionable cases and in cases in which prenatal detection in subsequent family members is desired.

Molecular testing is necessary to establish the diagnosis for two of the disorders, Muenke syndrome and *FGFR2*-related isolated coronal synostosis.

- Individuals with Muenke syndrome may have unilateral coronal synostosis or megalencephaly without craniosynostosis; diagnosis depends on identification of a disease-causing p.Pro250Arg mutation in *FGFR3*.
- *FGFR2*-related isolated coronal synostosis is characterized only by uni- or bicoronal craniosynostosis; diagnosis is based on identification of a disease-causing mutation in *FGFR2*.

The diagnosis of craniosynostosis and determination of the suture(s) involved are usually based on clinical findings and can be confirmed by a skull radiograph or head CT examination.

The phenotypes associated with FGFR-related craniosynostosis were clinically defined long before the molecular basis of this group of disorders was discovered (see Table 1).

Table 1. Distinguishing Clinical Features in the FGFR-Related Craniosynostosis Syndromes

Disorder	Thumbs	Hands	Great Toes	Feet
Muenke syndrome	Normal	± Carpal fusion	± Broad	± Tarsal fusion
Crouzon syndrome	Normal	Normal	Normal	Normal
Crouzon syndrome with acanthosis nigricans (AN)	Normal	Normal	Normal	Normal
Jackson-Weiss syndrome	Normal	Variable	Broad, medially deviated	Abnormal tarsals
Apert syndrome	Occasionally fused to fingers	Bone syndactyly	Occasionally fused to toes	Bone syndactyly
Pfeiffer syndrome	Broad, medially deviated	Variable brachydactyly	Broad, medially deviated	Variable brachydactyly
Beare-Stevenson syndrome	Normal	Normal	Normal	Normal
FGFR2-related isolated coronal synostosis	Normal	Normal	Normal	Normal

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Mutations in the *FGFR1*, *FGFR2*, and *FGFR3* genes cause *FGFR*-related craniosynostosis (Table 2).

Table 2. Molecular Basis of FGFR-Related Craniosynostosis Syndromes

Disorder	% of the Disorder Caused by *FGFR1* Mutations	% of the Disorder Caused by *FGFR2* Mutations	% of the Disorder Caused by *FGFR3* Mutations
Muenke syndrome			100%
Crouzon syndrome		100%	
Crouzon syndromewith acanthosis nigricans (AN)			100%
Jackson-Weiss syndrome		100%	
Apert syndrome		100%	
Pfeiffer syndrome type 1	5%	95%	
Pfeiffer syndrome type 2		100%	
Pfeiffer syndrome type 3		100%	
Beare-Stevenson syndrome		<100%	
FGFR2-related isolated coronal synostosis		100%	

Clinical testing

Sequence analysis. *FGFR1*, *FGFR2*, and *FGFR3* sequence analysis has high sensitivity for Apert syndrome and the isolated FGFR-related craniosynostosis syndromes *(FGFR2*-related isolated coronal synostosis and Muenke syndrome). The sensitivity of molecular testing is lower for the other disorders; its primary utility is in confirming questionable clinical diagnoses.

The yield of molecular genetic testing is higher in cases of bilateral than unilateral coronal synostosis [Mulliken et al 2004].

Table 3 summarizes molecular genetic testing for this disorder.

Table 3. Molecular Genetic Testing Used in the FGFR-Related Craniosynostosis Syndromes

Disorder	Test Method	Mutations Detected	Mutation Detection Frequency [1, 2]	Test Availability
Pfeiffer syndrome (type 1)	Sequence analysis	*FGFR1* sequence variants	67%	Clinical Testing
Apert syndrome		*FGFR2* sequence variants	>98%	Clinical Testing
Beare-Stevenson syndrome				
Crouzon syndrome			>50%	
FGFR2-related isolated coronal synostosis			100%	
Jackson-Weiss syndrome			Unknown	
Pfeiffer syndrome (all types)			67%	
Crouzon syndrome with acanthosis nigricans (AN)		*FGFR3* sequence alterations [3]	100%	Clinical Testing
FGFR3-related isolated coronal synostosis		*FGFR3* sequence variants		
Muenke syndrome	Targeted mutation analysis	*FGFR3* mutation [4]		

1. Proportion of affected individuals with a mutation(s) as classified by gene, disorder, and/or test method
2. Numbers reflect "sensitivity" (i.e., probability that an individual with the phenotype will have a positive result). No similar data exist for the positive predictive value of the test (i.e., probability that an individual with that test result would have the phenotype).
3. The mutation in Crouzon syndrome with AN is usually p.Ala391Glu.
4. Identification of the *FGFR3* mutation p.Pro250Arg is an obligate and defining feature of this disorder [Muenke et al 1997].

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To establish the diagnosis in a proband

- **Muenke syndrome** requires the combination of unilateral coronal synostosis or megalencephaly without craniosynostosis and identification of the p.Pro250Arg mutation in *FGFR3*.
- ***FGFR2*-related isolated coronal synostosis** requires the combination of uni- or bicoronal craniosynostosis and a disease-causing mutation in *FGFR2*.

To confirm the diagnosis in a proband

- **Crouzon syndrome with acanthosis nigricans** (AN) is usually caused by the *FGFR3* mutation p.Ala391Glu; therefore, the finding of AN in a young child with Crouzon syndrome should prompt testing for the p.Ala391Glu mutation in *FGFR3* before testing for *FGFR2* mutations. Choanal atresia, hydrocephalus, and the cranial features of Crouzon syndrome should suggest the diagnosis of Crouzon syndrome with AN even before AN appears. Subtle skeletal features such as narrow sacrosciatic notches, short vertebral bodies, lack of the normal increase in interpediculate distance

from the upper lumbar vertebrae caudally, and broad, short metacarpals and phalanges lend further support to this diagnosis [Schweitzer et al 2001].

- If testing is performed on a child with features of Crouzon syndrome during the first year of life (before the usual onset of AN), it is reasonable to test for *FGFR2* and *FGFR3* mutations concurrently.
- Testing for the *FGFR3* mutation p.Ala391Glu in a child older than age two years with Crouzon syndrome features without AN is likely to have a low yield.
- An algorithm to increase efficiency and cost-effectiveness of molecular testing in craniosynostosis disorders involves initial performance of sequence analysis of recurrent mutations, followed by selective gene sequencing [Chun et al 2003].

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies typically require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

Mutations in *FGFR1*, *FGFR2*, and *FGFR3* are responsible for a number of clinically distinct disorders.

FGFR1

- **Osteoglophonic dysplasia** is a skeletal dysplasia syndrome that shares characteristics with craniosynostosis syndromes and dwarfing syndromes. Features include craniosynostosis, prominent supraorbital ridge, depressed nasal root, rhizomelic dwarfism, and characteristic non-osseous bone lesions [White et al 2005]. The identification of pathogenic *FGFR1* mutations demonstrates that *FGFR1* may function as a negative regulator of long bone development rather than increasing skull bone growth [White et al 2005, Farrow et al 2006].
- An *FGFR1* mutation (p.Pro252Arg) has now been reported in three kindreds with the classic hand and foot findings of Pfeiffer syndrome but without craniosynostosis or craniofacial features [Hackett & Rowe 2006].

FGFR2

- A **familial scaphocephaly syndrome** characterized by scaphocephaly, macrocephaly, midface flattening, and mild intellectual disabilities has been reported in a three-generation kindred with a p.Lys526Glu mutation in *FGFR2*. This mutation resides in the tyrosine kinase-1 domain, which is located outside the typical mutational hot spot of the gene seen in other craniosynostosis syndromes [McGillivray et al 2005].
- **Saethre-Chotzen syndrome** is typically caused by *TWIST1* mutations, but a family with phenotypic features of Saethre-Chotzen syndrome and normal *TWIST1* sequence analysis had the *FGFR2* mutation p.Gln289Pro [Freitas et al 2006].
- **Syndromic craniosynostosis with elbow contracture.** The *FGFR2* mutation p.Ser351Cys has been reported in approximately eight individuals with severe craniosynostosis, midface hypoplasia, elbow joint contracture, developmental delays, and often premature death [Akai et al 2006].

FGFR3

- **Achondroplasia**

- **Hypochondroplasia**
- **Thanatophoric dysplasia**
- **Camptodactyly, tall stature, scoliosis, and hearing loss (CATSHL) syndrome** is caused by a p.Arg621His mutation in the *FGFR3* tyrosine kinase domain that leads to decreased protein function, indicating that mutations in *FGFR3* can either hinder or promote bone growth [Toydemir et al 2006].

Note: *FGFR3* mutations were reported in two individuals with both Muenke syndrome and hypochondroplasia. Both were cognitively normal but had early-onset temporal lobe seizures and bilateral dysgenesis of the medial temporal lobes [Grosso et al 2003].

Clinical Description

Natural History

The abnormal skull shape in the FGFR-related craniosynostosis syndromes is usually noted in the newborn period; occasionally, it may be detected either prenatally by ultrasound examination or not until later in infancy. Because the skull grows in planes perpendicular to the cranial sutures, premature suture closure causes skull growth to cease in the plane perpendicular to the closed suture and to proceed parallel to the suture. The skull shape becomes asymmetric, with the shape depending on which suture(s) is (are) closed. Coronal craniosynostosis causes the skull to be turribrachycephalic, or "tower shaped." Occasionally, cloverleaf skull (called *Kleeblatschadel*) is seen. Cloverleaf skull involves a trilobar skull deformity usually caused by synostosis of coronal, lambdoidal, metopic, and sagittal sutures. The brain protrudes through open anterior and parietal fontanels.

The characteristic facial features shared by all of the FGFR-related craniosynostosis syndromes (except Muenke and *FGFR2*-related isolated coronal synostosis) finclude: ocular hypertelorism, proptosis, midface hypoplasia, small beaked nose, and prognathism. A high-arched palate is often present; more rarely, a cleft palate is present. Choanal stenosis or atresia can be seen, as well as sensorineural hearing loss and visual problems including strabismus. Cloverleaf skull is accompanied by midface hypoplasia, down-slanting palpebral fissures, and extreme proptosis; in addition, developmental delay and/or mental retardation, hydrocephalus, hearing loss, and visual impairment are common.

Breathing problems can occur in the first few months of life because of upper-airway obstruction related to the midface hypoplasia and associated choanal atresia or stenosis. In severe cases, these problems may present as life-threatening respiratory failure or as failure to thrive resulting from poor feeding. In either case, tracheostomy is often needed. Non-communicating hydrocephalus is another complication that can result in neurologic impairment or death if not diagnosed and treated at an early stage. The risk of intracranial hypertension is greatest in Crouzon syndrome [Renier, Lajeunie et al 2000]. Even if every medical complication is managed promptly, a proportion of affected children will develop mental retardation and neurologic problems. The greatest risk for mental retardation is found in Apert syndrome [Renier, Lajeunie et al 2000]. Overall, the risk for significant problems depends on the associated anomalies in the individual rather than on the specific syndrome.

Specific clinical features of each of the FGFR-related craniosynostosis syndromes are summarized below.

Muenke syndrome. Phenotypic overlap occurs with Pfeiffer, Jackson-Weiss, and Saethre-Chotzen syndromes. Some individuals with a disease-causing mutation have no clinically fapparent abnormalities and are identified only on clinical, radiographic, or molecular genetic evaluation after they give birth to an affected child.

- **Intellect.** Normal
- **Craniofacial.** Variable. Uni- or bilateral coronal craniosynostosis, or only megalencephaly; mild to significant midface hypoplasia; ocular hypertelorism
- **Extremities.** Variable. Carpal-tarsal fusion is diagnostic when present but is not always present; brachydactyly, carpal bone malsegregation, or coned epiphyses may occur.

Crouzon syndrome

- **Intellect.** Normal
- **Craniofacial.** Significant proptosis, external strabismus, mandibular prognathism
- **Extremities.** Normal (although radiographic metacarpal-phalangeal profile may reveal shortening) [Murdoch-Kinch & Ward 1997]
- **Other.** Progressive hydrocephalus (30%), often with tonsillar herniation; sacrococcygeal tail has also been described [Lapunzina et al 2005]

Crouzon syndrome with acanthosis nigricans (AN)

- **Intellect.** Normal
- **Craniofacial.** Significant proptosis, external strabismus, mandibular prognathism
- **Extremities.** Normal (although radiographic metacarpal-phalangeal profile may reveal shortening) [Murdoch-Kinch & Ward 1997]
- **Cutaneous.** The 5% of individuals with Crouzon syndrome who have AN (pigmentary changes in the skin fold regions) are said to have Crouzon syndrome with AN. AN can be present in the neonatal period or appear later.

Jackson-Weiss syndrome

- **Intellect.** Normal
- **Craniofacial.** Mandibular prognathism
- **Extremities.** Broad and medially deviated great toes, with normal hands; short first metatarsal, calcaneocuboid fusion, abnormally formed tarsals

Apert syndrome

- **Intellect.** Varying degrees of developmental delay/mental retardation (50%), possibly related to the timing of craniofacial surgery [Renier et al 1996]
- **Craniofacial.** Turribrachycephalic skull shape; moderate-to-severe midface hypoplasia
- **Extremities.** Soft tissue and bony ('mitten glove') syndactyly of fingers and toes involving variable number of digits; occasional rhizomelic shortening, elbow ankylosis
- **Other.** Fused cervical vertebrae (68%), usually C5-C6; hydrocephalus (2%); occasional internal organ anomalies [Cohen & Kreiborg 1993]

Pfeiffer syndrome. Pfeiffer syndrome has been subdivided into three clinical types [Cohen 1993]; types 2 and 3 are more common and more severe than type 1.

Pfeiffer syndrome type 1

- **Intellect.** Usually normal

- **Craniofacial.** Moderate-to-severe midface hypoplasia
- **Extremities.** Broad and medially deviated thumbs and great toes; variable degree of brachydactyly. In one family, reported involvement of the feet was the only abnormality [Rossi et al 2003].
- **Other.** Hearing loss and hydrocephalus can be seen. Overall prognosis is more favorable than in Pfeiffer syndrome types 2 and 3.

Pfeiffer syndrome type 2

- **Intellect.** Developmental delay/mental retardation common
- **Craniofacial.** Cloverleaf skull, extreme proptosis (often unable to close eyelids)
- **Extremities.** Broad and medially deviated thumbs and great toes; ankylosis of elbows, knees; variable degree of brachydactyly
- **Other.** Choanal stenosis/atresia, laryngotracheal abnormalities; hydrocephalus; seizures; sacrococcygeal eversion [Oliveira et al 2006]; increased risk for early death

Pfeiffer syndrome type 3

- **Intellect.** Developmental delay/mental retardation common
- **Craniofacial.** Turribrachycephalic skull shape, extreme proptosis (often unable to close eyelids)
- **Extremities.** Broad and medially deviated thumbs and great toes; ankylosis of elbows, knees; variable degree of brachydactyly
- **Other.** Choanal stenosis/atresia, laryngotracheal abnormalities; hydrocephalus; seizures, increased risk for early death

Beare-Stevenson cutis gyrata

- **Intellect.** All have mental retardation
- **Craniofacial.** Moderate-to-severe midface hypoplasia; abnormal ears, natal teeth
- **Extremities.** Normal; furrowed palms and soles
- **Cutaneous.** Widespread cutis gyrata and AN, which are usually evident at birth; skin tags, prominent umbilical stump, accessory nipples
- **Genital.** Bifid scrotum, prominent labial raphe, rugated labia majora
- **Other.** Pyloric stenosis; anterior anus

***FGFR2*-related isolated coronal synostosis**

- **Intellect.** Normal
- **Craniofacial.** Unilateral coronal synostosis
- **Extremities.** Normal

Genotype-Phenotype Correlations

A wide phenotypic range has been described among individuals with identical mutations in *FGFR2* [Mulliken et al 1999, Ito et al 2005]. Mutations in *FGFR2* or *FGFR3* can give rise to either bilateral or unilateral coronal synostosis, even in the same family [Mulliken et al 2004]. In a study of 47 individuals with unilateral coronal synostosis (also known as synostotic frontal plagiocephaly), asymmetric brachycephaly and orbital hypertelorism were strongly

correlated with identification of a mutation in *FGFR2, FGFR3*, or *TWIST1* (formerly *TWIST*) [Mulliken et al 2004].

One specific genotype-phenotype correlation is the association of the p.Ala391Glu mutation in the *FGFR3* gene in individuals with Crouzon syndrome and AN. Individuals with Crouzon syndrome who do not have AN are unlikely to have a mutation in *FGFR3*.

Cleft palate, severe ocular problems (strabismus, ptosis, astigmatism, and amblyopia), nasolacrimal stenosis, and possibly humeroradial synostosis are more common in individuals with the p.Ser252Trp mutation in *FGFR2* [Akai et al 2006], whereas the degree of syndactyly and mental impairment is more prominent in individuals with the p.Pro253Arg mutation in *FGFR2* [Slaney et al 1996, Lajeunie et al 1999, Kanauchi et al 2003, Jadico et al 2006]. Individuals with Apert syndrome and the p.Pro253Arg mutation have a more improved craniofacial appearance following craniofacial surgery [von Gernet et al 2000].

Mutations seen in individuals with Crouzon, Pfeiffer, and Jackson-Weiss syndromes occur in and around the B exon of the third immunoglobulin-like domain in *FGFR2*.

Identical mutations have been seen in individuals with Crouzon, Pfeiffer, and Jackson-Weiss syndromes [Hollway et al 1997, Oldridge et al 1997], suggesting that unlinked modifier genes or epigenetic factors play a role in determining the final phenotype. Interestingly, two *FGFR2* mutations creating cysteine residues (p.Trp290Cys and p.Tyr340Cys) cause severe forms of Pfeiffer syndrome whereas conversion of the same residues into another amino acid (p.Trp290Gly/Arg, p.Tyr340His) results exclusively in the Crouzon phenotype [Lajeunie et al 2006].

Pfeiffer syndrome-causing mutations p.Ser352Cys, p.Ser351Cys, p.Trp290Cys, p.Tyr342Arg, and p.Cys342Arg in *FGFR2* have been associated with severe phenotypes including cloverleaf skull, severe exophthalmia, midface flattening, hydrocephalus requiring ventriculoperitoneal shunt, radio-ulnar-humeral synostosis, fusion of the cartilaginous tracheal rings (tracheal sleeve), and frequently premature death [Zackai et al 2003, Hockstein et al 2004, Gonzales et al 2005, Akai et al 2006, Lajeunie et al 2006, Oliveira et al 2006, Stevens & Roeder 2006].

Three individuals were reported to have clinical features of Crouzon, Pfeiffer, or Apert syndromes, but had mutations in both *FGFR2* and *TWIST1* [Anderson et al 2006].

Penetrance

FGFR-related coronal synostosis is usually autosomal dominant with reduced penetrance.

Jackson-Weiss, Apert, and Pfeiffer syndromes show complete penetrance.

Crouzon syndrome typically implies complete penetrance; however, in one family a *de novoFGFR2* mutation was associated with variable expressivity and reduced penetrance [de Ravel et al 2005].

Anticipation

There have been no reports of anticipation in the FGFR-related craniosynostosis syndromes.

Nomenclature

Adelaide-type craniosynostosis, a term to describe Muenke syndrome, is no longer used.

Prevalence

The overall incidence for all forms of craniosynostosis is 1:2000-1:2500 live births.

The incidence of coronal synostosis is 1:16,000 in males and 1:8000 in females; the overall contribution of *FGFR* gene mutations to the incidence of craniosynostosis is unknown.

The incidence of Crouzon syndrome is 1.6:100,000; that of Apert syndrome is 1:100,000; the combined incidence of the Pfeiffer syndromes is 1:100,000.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Primary craniosynostosis needs to be distinguished from secondary craniosynostosis. In primary craniosynostosis, abnormal biology of the suture causes premature suture closure, as in the FGFR-related craniosynostoses; in secondary craniosynostosis, the suture biology is normal, but abnormal external forces result in premature suture closure. In children with deficient brain growth, all cranial sutures fuse and the head is symmetric and microcephalic. Abnormal head positioning in utero or in infancy may produce an abnormal skull shape (plagiocephaly); the abnormality often resolves with appropriate head positioning but occasionally results in craniosynostosis [Hunt & Puczynsk 1996, Kane et al 1996].

In individuals with primary craniosynostosis it is important to determine which cranial sutures are involved and whether the craniosynostosis is an isolated finding or part of a syndrome.

- **Lambdoidal or sagittal synostosis** suggests a diagnosis other than FGFR-related craniosynostoses, even in the presence of hand and foot anomalies (e.g., sagittal synostosis and cutaneous hand and foot syndactyly in Philadelphia-type craniosynostosis [Robin et al 1996]).
- **Metopic synostosis,** which causes trigonocephaly, is usually an isolated finding, but may be part of a more complex disorder in which progressive involvement of other sutures occurs [Tartaglia et al 1999]. Therefore, *FGFR* molecular genetic testing is not warranted in individuals with isolated trigonocephaly, but is a consideration in individuals with trigonocephaly in whom other craniofacial anomalies are seen. A recent study found no pathologic mutations in *FGFR1*, *CER1*, or *CDON* in individuals with either syndromic or nonsyndromic metopic craniosynostosis, suggesting that analysis of these genes is not warranted in persons with these findings [Jehee et al 2006].

Isolated craniosynostosis (i.e., craniosynostosis occurring without other anomalies) accounts for the vast majority of craniosynostosis. Only rarely is isolated craniosynostosis familial, but in such cases it is usually autosomal dominant with reduced penetrance, with the recurrence risk dependent on which suture is involved [Cohen 1996, Lajeunie et al 1996].

The incidence of *FGFR3* disease-causing mutations in individuals with apparently isolated coronal craniosynostosis is not known.

- One study found an *FGFR3* mutation in four of 37 individuals with nonsyndromic coronal craniosynostosis; in three of the four individuals, the father had the *FGFR3* mutation [Gripp et al 1998].
- In another study, 29 of 76 individuals with isolated coronal synostosis had the *FGFR3* mutation p.Pro250Arg.

- In another study, eight of 47 individuals with unilateral coronal synostosis had identifiable mutations, including two in *FGFR2*, three in *FGFR3*, and three in *TWIST1* [Mulliken et al 2004]. Therefore, testing of all individuals with either unilateral or bilateral coronal craniosynostosis for *FGFR2* or *FGFR3* mutations is probably warranted, particularly if asymmetric brachycephaly and/or orbital hypertelorism are present [Renier, El Ghouzzi et al 2000].

Syndromic craniosynostosis. Craniosynostosis is a finding in more than 150 genetic disorders. Additional syndromes that should be considered:

- **Saethre-Chotzen syndrome**. Classic Saethre-Chotzen syndrome is characterized by coronal synostosis (unilateral or bilateral), facial asymmetry (particularly in individuals with unicoronal synostosis), ptosis, and characteristic appearance of the ear (small pinna with a prominent crus). Syndactyly of digits two and three of the hand is variably present. Although mild to moderate developmental delay and mental retardation have been reported, normal intelligence is more common. Less common manifestations of Saethre-Chotzen syndrome include short stature, parietal foramina, radioulnar synostosis, cleft palate, maxillary hypoplasia, ocular hypertelorism, hallux valgus, and congenital heart malformations. The diagnosis of Saethre-Chotzen syndrome is made primarily on clinical findings. Mutations in *TWIST1* are causative. Inheritance is autosomal dominant.

  Several features are shared by Saethre-Chotzen syndrome and Muenke syndrome. However, persons with Saethre-Chotzen syndrome with a *TWIST1* mutation typically have a lower frontal hairline, worsening ptosis, soft-tissue syndactyly, hallux valgus, and increased cranial pressure resulting from early suture fusion. Persons with Muenke syndrome have an increased frequency of hearing loss and mental disabilities [Kress et al 2006]. The clinical diagnosis of Saethre-Chotzen syndrome has also been reported in a family with an *FGFR2* mutation (p.Gln289Pro), suggesting that the *TWIST1* and *FGFR* gene products may interact during development [Freitas et al 2006]. Testing for suspected Saethre-Chotzen syndrome should include analysis of *FGFR2*, *FGFR3*, and *TWIST1*.

- **Boston-type craniosynostosis.** From the 19 affected individuals in the one family reported to date [Warman et al 1993], four general phenotypes emerged:
  - Type 1. Fronto-orbital recession (8 individuals)
  - Type 2. Frontal bossing (2)
  - Type 3. Turribrachycephaly as a result of coronal craniosynostosis (7)
  - Type 4. Cloverleaf skull (2)

Short first metatarsals are present. Headaches, seizures, myopia, and visual deficits may occur. Of note, some individuals who have a disease-causing mutation are asymptomatic. Mutations in *MSX2* are causative [Ignelzi et al 2003]. Inheritance is autosomal dominant, with complete penetrance and variable expression. This disorder is apparently rare; Wilkie & Mavrogiannis (2004) found no *MSX2* mutation in 211 individuals with craniosynostosis of unknown cause who had no mutations identified in other major genes.

- **Antley-Bixler syndrome** (trapezoidocephaly-multiple synostosis syndrome) is caused by a sterol biosynthesis defect and involves premature closure of the coronal and lambdoidal sutures, brachycephaly with frontal bossing, proptosis, downslanting palpebral fissures, severe depression of the nasal bridge (with or without choanal stenosis or atresia), and low-set, protruding ears. The main limb features are radiohumeral synostosis, medial bowing of the ulnae, bowing of the femora, slender

hands and feet, contractures at the proximal IP joints, fractures, and advanced bone age. Some individuals have congenital heart disease, renal anomalies, abnormalities of the female genitalia, and signs of congenital adrenal hyperplasia [Bottero et al 1997, Williamson et al 2006]. Mutations in the gene encoding cytochrome P450 reductase *(POR*) are causative [Adachi et al 2006, Marohnic et al 2006]. Inheritance is autosomal recessive.

- **Baller-Gerold syndrome** is a craniosynostosis syndrome with radial aplasia. The craniosynostosis usually involves the coronal sutures but may affect multiple sutures. The radial defect may be asymmetric, resulting in aplasia on one side and hypoplasia on the other. The thumb can be absent and the ulna is usually short and curved. Carpal and metacarpal bones may be absent. Occasional findings include ocular hypertelorism, epicanthic folds, a prominent nasal bridge, midline capillary hemangiomas, genitourinary malformations, and mental retardation. Identification of *RECQL4* mutations in two unrelated families supports the notion that Baller-Gerold syndrome is allelic to Rothmund-Thomson syndrome and RAPADILINO syndrome, and that mutations in *RECQL4* cause a subset of Baller-Gerold syndrome [Van Maldergem et al 2006]. Inheritance is autosomal recessive.
- **Carpenter syndrome** (acrocephalopolysyndactyly type II) is a craniosynostosis syndrome with preaxial polydactyly of the feet. Brachydactyly, syndactyly, and aplasia or hypoplasia of the middle phalanges are present in the hands. Mental retardation is variable. The causative gene is *RAB23* [Jenkins et al 2007]. Inheritance is autosomal recessive.
- **Craniofrontonasal syndrome** is characterized by premature closure of the coronal suture and frontonasal dysplasia. Features include severe ocular hypertelorism, a broad bifid nose, asymmetric frontal bossing, a low posterior hairline, anterior widow's peak, and occasionally a cleft lip and palate, neck webbing, rounded shoulders, abnormal clavicles, and raised scapulae. Longitudinal splitting of the nails occurs often, skin syndactyly is occasionally present, and the fingers and toes may be deviated distally or occasionally hypoplastic. Most children have normal intelligence. More females have been reported than males, with more severe manifestations in females [Saavedra et al 1996]. Mutations in *EFNB1* are causative. Inheritance is X-linked dominant.
- **Greig cephalopolysyndactyly** features include high forehead with frontal bossing, macrocephaly, hypertelorism, broad nasal base, polydactyly of the hands (often postaxial), and feet with syndactyly of toes 1, 2, and 3 and often a duplicated halux. [Biesecker 1997]. Mutations in *GLI3* are causative. Standard Giemsa-banding cytogenetic studies may detect translocations or gross cytogenetic deletions involving 7p13. FISH analysis detects deletions in the estimated 5%-10% of individuals with large deletions. Inheritance is autosomal dominant.
- **Opitz trigonencephaly C syndrome** is a multiple malformation syndrome with trigonocephaly. The causative gene is not known, but one person has been reported to have a *de novo* balanced reciprocal translocation t(3;18)(q13.13;q12.1) [Chinen et al 2006]. Inheritance is autosomal recessive.
- **Philadelphia-type craniosynostosis,** featuring sagittal suture craniosynostosis with cutaneous hand and foot syndactyly, was identified in a single large kindred [Robin et al 1996]. The causative gene is not known. Inheritance is autosomal dominant.
- **Shprintzen-Goldberg syndrome** (marfanoid-craniosynostosis syndrome) is characterized by craniosynostosis (involving the coronal, sagittal, or lambdoid sutures), distinctive craniofacial features, skeletal changes (dolichostenomelia,

arachnodactyly, camptodactyly, pes planus, pectus excavatum or carinatum, scoliosis, joint hypermobility, or contractures), neurologic abnormalities, mild to moderate mental retardation, and brain anomalies (hydrocephalus, dilatation of the lateral ventricles, and Chiari 1 malformation). Cardiovascular anomalies (mitral valve prolapse, mitral regurgitation, and aortic regurgitation) may occur. Minimal subcutaneous fat, abdominal wall defects, cryptorchidism in males, and myopia are also characteristic findings. The diagnosis is suspected in individuals with characteristic clinical findings and radiographic findings showing C1-C2 abnormality, wide anterior fontanel, thin ribs, 13 pairs of ribs, square-shaped vertebral bodies, and osteopenia. The causative gene and mode of inheritance are unknown.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with FGFR-related craniosynostosis, the following evaluations are recommended:

- Assessment for hydrocephalus by brain CT or MRI in all cases of syndromic craniosynostosis, with close observation in those with mutations known to have a more severe phenotype
- Assessment for upper-airway obstruction or tracheal sleeve (in *FGFR2*-related Pfeiffer syndrome)
- Assessment for exposure keratopathy
- Spinal x-rays to evaluate for vertebral anomalies

Treatment of Manifestations

Craniofacial. Children with any of the FGFR-related craniosynostosis syndromes benefit from the multidisciplinary team approach practiced in most craniofacial clinics affiliated with major pediatric medical centers. The specialists usually include plastic surgeons, neurosurgeons, otolaryngologists, and dentists as well as audiologists, speech pathologists, developmental pediatricians, social workers, and medical geneticists. The team can usually identify and address physical and developmental problems as well as psychosocial and other issues.

Individuals with syndromic craniosynostosis usually require a series of staged surgical procedures; the number and type are tailored to the individual's needs [Posnick & Ruiz 2000]. Three-dimensional skull CT can be used for morphologic mapping to help plan surgical treatment [Binaghi et al 2000]. Some individuals with syndromic craniosynostosis require a dozen or more surgeries over a lifetime. Seldom is the correction perfect, but significant cosmetic improvement is often possible. Evidence suggests that the calvarial bone needed for these surgeries is often more brittle, thinner, and less robust than cranial bone from unaffected donors [Tholpady et al 2004].

In contrast to children with nonsyndromic craniosynostosis, in whom the first surgery is usually performed between ages six months and one year, children with syndromic craniosynostosis often have their first surgery as early as age three months. The procedure is a bilateral craniotomy with a fronto-orbital advancement to expand the cranial vault. Because the procedure leaves uncovered areas of dura that fill in by age 15-18 months, it must be performed before the child is 18 months old. In a series of 2,317 individuals who underwent surgery for craniosynostosis, improved cosmetic and functional results followed early surgery; no increased operative risk was seen in infants [Renier, Lajeunie et al 2000].

Distraction osteogenesis of the craniofacial skeleton and long bones of the extremities may be a less invasive alternative approach to bone grafting in some individuals. In addition, the distraction procedures can expand the overlying soft tissues simultaneously. The devices used for distraction of the mandible, midface, and cranium tend to be the buried type and made of absorbable materials; cytokine administration may shorten the consolidation period. The usefulness and appropriateness of the distraction procedure must be assessed for each disorder [Matsumoto et al 2003].

In some cases, other complications including hydrocephalus, upper-airway obstruction, and exposure keratopathy of the cornea may prompt even earlier craniotomy or fronto-orbital advancement, or other interventions including ventriculo-peritoneal stunting, tracheostomy, or surgical eyelid closure.

Timing of subsequent craniofacial surgeries influences their success. Procedures done prior to the cessation of growth in the particular facial region usually have poor long-term results and require additional operations.

Individuals with Apert syndrome have the highest incidence of repeat surgery to correct forehead contour [Wong et al 2000, Thomas et al 2005].

Spine. Congenital spine anomalies can cause scoliosis and spinal injury and thus need immediate attention.

Limbs. Surgical correction of limb defects is usually not possible because the skeletal anomalies are developmental and the structures have never formed normally.

- In the mitten-glove syndactyly seen in Apert syndrome, surgical separation of the digits often provides relatively little functional improvement.
- With the elbow ankylosis seen in Pfeiffer syndrome types 2 and 3, some functional improvement can be gained by altering the angle at which the elbows are fixed. For example, in most affected individuals, elbow contractures are at approximately the same angle, often so that an individual cannot reach the mouth easily with the hands or clean appropriately following toileting; functional improvement can be achieved if the angle of each arm is altered so that one arm is positioned for eating and the other for toileting.

Prevention of Secondary Complications

The primary treatment of craniofacial abnormalities associated with craniosynostosis is surgical reconstruction. Early treatment may reduce the risk for secondary complications (e.g., hydrocephalus, cognitive impairment).

Patients with severe proptosis often require ophthalmologic lubrication to prevent exposure keratopathy.

Surveillance

Six of 29 persons with the *FGFR3* mutation p.Pro250Arg required reoperation for increased intracranial pressure, emphasizing the need for continued long-term monitoring [Thomas et al 2005].

Persons with a known risk for significant complications, including hydrocephalus, should be monitored from birth throughout life at intervals and by methods appropriate for the severity of the clinical findings.

Testing of Relatives at Risk

At-risk relatives should be evaluated by clinical and radiographic criteria given that manifestations may not be readily evident in all affected individuals. When the disease-causing mutation is known in the family, molecular genetic testing can be used to evaluate relatives for the disorder. Early diagnosis may allow mildly affected relatives to benefit from early surveillance and intervention.

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

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

FGFR-related craniosynostosis is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- An individual with FGFR-related craniosynostosis may have an affected parent or may have the disease as the result of a *de novo* gene mutation.

- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include clinical, radiographic, and molecular genetic evaluation.
- With a milder phenotype, as can be seen in Muenke syndrome, Crouzon syndrome, Pfeiffer syndrome, and Jackson-Weiss syndrome, inheritance of the disease-causing mutation from an affected parent is common; whereas in the most severe forms, *de novo* gene mutations are common.
- All cases of Pfeiffer syndrome 3 and Beare-Stevenson syndrome and all but one case of Pfeiffer syndrome 2 have resulted from *de novo* gene mutations.
- Advanced paternal age has been shown clinically to be associated with *de novo* mutations for Crouzon syndrome, Apert syndrome, Pfeiffer syndrome [Glaser et al 2000], Beare-Stevenson syndrome, and Muenke syndrome [Rannan-Eliya et al 2004]. Paternal age effect in *de novo* mutations has been conclusively demonstrated at the molecular level in Apert syndrome [Moloney et al 1996]. It has been proposed that *FGFR* mutations are paradoxically enriched in the male germline because they confer a selective advantage to the spermatagonial cells in which they arise [Goriely et al 2003].
- *FGFR3*-related isolated coronal synostosis is usually inherited in an autosomal dominant manner with reduced penetrance.

Sibs of a proband

- The risk to sibs of the proband depends on the genetic status of the parents.
- If a parent is affected or has a disease-causing mutation, the risk is 50%.
- When the disease-causing mutation cannot be detected in the DNA of either parent, the risk to sibs of a proband is low, but greater than that of the general population because of the possibility of germline mosaicism.

Offspring of a proband. Affected individuals have a 50% chance of passing the disease-causing mutation to each child.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected or to have a disease-causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

See Testing of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Each syndrome is usually consistent within an individual family; for example, if a parent has the clinical findings of Pfeiffer syndrome, he or she has a 50% chance of having a child with Pfeiffer syndrome rather than Crouzon, Jackson-Weiss, or Apert syndrome. Nontheless, rare examples exist in which the phenotype of affected individuals in a given family has varied: some family members had findings suggestive of Pfeiffer syndrome, whereas others had findings suggestive of Jackson-Weiss or Crouzon syndromes [Meyers et al 1996, Steinberger et al 1996, Hollway et al 1997, Steinberger et al 1997].

Considerations in families with an apparent *de novo* mutation. When the parents of a proband with an autosomal dominant condition are unaffected and/or do not have a disease-causing mutation, possible non-medical explanations including alternate paternity or undisclosed adoption could be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal 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. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

High-risk pregnancies. Prenatal diagnosis for pregnancies at 50% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Low-risk pregnancies. In a pregnancy not previously identified to be at risk for craniosynostosis in which an abnormal skull shape is detected on prenatal ultrasound examination, prenatal testing is more difficult. While testing for mutations in the *FGFR1*, *FGFR2*, or *FGFR3* genes is possible, the yield is likely to be low. Furthermore, identification of a mutation 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). Three-dimensional ultrasound, three-dimensional CT scan, or MRI has proven useful in some cases to further delineate suspicious ultrasound findings and assess for underlying brain abnormalities [Benacerraf et al 2000, Mahieu-Caputo et al 2001, Hansen et al 2004, Itoh et al 2006]. Indeed, prenatal MRI is often used to accurately diagnosis suspected craniosynostosis syndromes such as Pfeiffer or Apert syndromes. Detectable MRI findings may include agenesis of the corpus callosum, hydrocephalus, or cloverleaf skull [Itoh et al 2006, Quintero-Rivera et al 2006].

Requests for prenatal testing for conditions such as FGFR-related craniosynostoses that have treatment available are not common. 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Craniosynostosis Syndromes, FGFR-Related

Gene Symbol	Chromosomal Locus	Protein Name
FGFR1	8p11.2-p11.1	Basic fibroblast growth factor receptor 1
FGFR2	10q26	Fibroblast growth factor receptor 2
FGFR3	4p16.3	Fibroblast growth factor receptor 3

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Craniosynostosis Syndromes, FGFR-Related

101200	APERT SYNDROME
101600	PFEIFFER SYNDROME
123150	JACKSON-WEISS SYNDROME; JWS
123500	CROUZON SYNDROME
123790	CUTIS GYRATA SYNDROME OF BEARE AND STEVENSON
134934	FIBROBLAST GROWTH FACTOR RECEPTOR 3; FGFR3
136350	FIBROBLAST GROWTH FACTOR RECEPTOR 1; FGFR1
176943	FIBROBLAST GROWTH FACTOR RECEPTOR 2; FGFR2
602849	MUENKE SYNDROME

Table C. Genomic Databases for Craniosynostosis Syndromes, FGFR-Related

Gene Symbol	Entrez Gene	HGMD
FGFR1	2260 (MIM No. 136350)	FGFR1
FGFR2	2263 (MIM No. 176943)	FGFR2
FGFR3	2261 (MIM No. 134934)	FGFR3

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

The fibroblast growth factors (FGFs) are a family of at least 22 known signaling molecules that function to regulate cell proliferation, differentiation, and migration through a variety of complex pathways [Wilkie 1997, Coumoul & Deng 2003]. They are important in angiogenesis, wound healing, limb development, mesoderm induction and patterning neuronal differentiation, and malignant transformation. They act through the fibroblast growth factor receptors (FGFRs), a family of four tyrosine kinase receptors that bind the FGFs in a nonspecific manner (any FGF can bind to any FGFR).

The FGFRs share the general structure of a split cytoplasmic tyrosine kinase domain, a transmembrane domain, and an extracellular domain that contains three immunoglobulin (Ig)-like domains. Ligand binding occurs at the second and third Ig-like domains. After binding an FGF, an FGFR dimerizes with another FGFR through a series of cysteine residues in these Ig-like domains. Dimerization promotes activation of the tyrosine kinase, which initiates a complex cascade of intracellular signals including activation of *Runx2*, a key transcription factor in osteoblast differentiation [Baroni et al 2005, Kim et al 2006]. Both ligand binding and dimerization are nonspecific, with any type of FGFR binding to any FGF and then dimerizing with any FGFR.

The FGF/FGFR system achieves its specificity through temporal and spatial variations in expression patterns. Additional diversity is created by alternative splicing of exons of the *FGFR*s, exemplified by exon 7 of *FGFR2* [Ornitz 2005]. A p.Cys278Phe mutation in *FGFR2* decreases protein glycosylation while increasing degradation, demonstrating that FGFR2 localization and autoactivation is glycosylation dependent [Hatch et al 2006].

Mutations in *FGFR1*, *FGFR2*, and *FGFR3* have been associated with a variety of clinical phenotypes. To date, no evidence linking *FGFR4* to craniofacial or skeletal disorders exists [Gaudenz et al 1998]. Interestingly, the same mutation in either *FGFR1*, *FGFR2*, or *FGFR3* results in different clinical craniosynostosis syndromes, thus implicating a common pathologic mechanism with FGFR gain of function in Pfeiffer, Apert, Muenke, and Beare-Stevenson syndromes [Wilkie et al 2001]. FGF9 binding is enhanced in the *FGFR1* Pfeiffer-related mutation p.Pro252Arg and the *FGFR3* Muenke-related mutation p.Pro250Arg; thus, FGF9 may be a potential pathophysiologic ligand for mutant FGFRs in mediating craniosynostosis [Ibrahimi et al 2004]. Differences in the primary sequence among FGFRs result in varying effects on ligand binding specificity [Ibrahimi et al 2004].

The normal function of the FGFRs appears to be to restrain limb growth, as *FGFR3* knockout mice have elongated tails and hindlimbs [Colvin et al 1996, Deng et al 1996]. This phenomenon suggests that *FGFR* mutations are hypermorphic, causing the gene product to perform its normal function excessively. The exact mechanism of the hypermorphic effect is different for different types of mutations that have been reported in the FGFR-related craniosynostosis syndromes (reviewed in Wilkie 1997).

It appears that the diseases caused by *FGFR2* mutations in these clinically distinct syndromes may be points along a continuum of a phenotypic spectrum. Evidence to support this concept comes from reports of clinically unique phenotypes caused by *FGFR2* mutations. An example is the phenotype of the family reported by Steinberger et al (1996) with an *FGFR2* mutation previously associated with Crouzon syndrome but not consistent with any of the *FGFR2*-related craniosynostosis syndromes (i.e., Apert, Crouzon, Pfeiffer, and Jackson-Weiss). Affected family members lacked the broad and medially deviated thumbs of Pfeiffer syndrome. Only one of nine had broad great toes, but they were not medially deviated as one would expect with Jackson-Weiss syndrome. In addition, significant midfacial hypoplasia and ocular proptosis were not present, as would be expected with Crouzon syndrome.

***FGFR1*—Normal allelic variants:** *FGFR1* has a genomic size of approximately 58 kb. Several mRNA splice variants produce seven isoforms. Isoform 1 contains 18 total exons (17 coding exons) and has the largest mRNA product.

Pathologic allelic variants: A single common mutation, p.Pro252Arg, in the linker region between the second and third Ig-like domains of *FGFR1* has been associated in five unrelated families with a relatively mild form of Pfeiffer syndrome type 1. *FGFR1* mutations have also been associated with Jackson-Weiss syndrome, osteoglophonic dysplasia, and autosomal dominant Kallmann syndrome. See Genomic Databases table.

Normal gene product: Basic fibroblast growth factor receptor 1 (FGFR1) has three extracellular Ig-like domains (only two of which are active), a transmembrane domain, and a split tyrosine kinase intracellular domain. The Ig-like domains function in promiscuous ligand binding: any FGFR binds any FGF. With ligand binding, two FGFRs dimerize and activate the tyrosine kinase, initiating an intracellular cascade. Basic FGFR1 and FGFR2 mRNA is found during embryogenesis in cartilage and bone precursors that will form the craniofacial and apical skeleton [Muenke & Schell 1995]. In the apical skeleton, basic FGFR1 is expressed

throughout the entire developing limb bud, whereas FGFR2 is primarily expressed in the outer ectodermal layer.

Abnormal gene product: No functional studies have been done on the *FGFR1* receptor mutation p.Pro252Arg, but studies have been done on the analogous mutations seen in both *FGFR2* and *FGFR3*. Like the mutations seen in *FGFR2* and *FGFR3,* the *FGFR1* mutation is dominant, so that the altered protein's effect is seen even in the presence of the normal second allele. Based on a number of studies on fibroblasts and animal models containing *FGFR* mutations, the effect seems to be one of excess activity; i.e., the mutant receptors work better than the wild type. The p.Pro252Arg mutation occurs in the region between the second and third Ig-like loops, a site that is thought to be important in ligand binding. The substitution of the bulkier residue is thought to change the configuration of the site, thereby altering ligand binding. The increased affinity of the receptor for ligand causes excessive activity, which may then promote excessive receptor down-regulation (summarized in Wilkie 2005).

***FGFR2*—Normal allelic variants:** *FGFR2* contains approximately 120 kb of genomic DNA with 18 total exons (17 coding exons). Alternative splicing produces two isoforms, where isoform 2 is one amino acid longer than isoform 1.

Pathologic allelic variants: Most *FGFR2* mutations are missense mutations, although small insertions, deletions, and splice site mutations have also been reported. No nonsense or frameshift mutations have been reported [Wilkie 1997]. Mutations in *FGFR2* have been associated with a variety of phenotypes including Apert, Crouzon, Pfeiffer, Jackson-Weiss, and Beare-Stevenson [Przylepa et al 1996] syndromes. In addition, a novel heterozygous mutation was found in a family in which the proband, who displayed intrauterine constraint, had nonsyndromic unicoronal synostosis and other family members had only mild facial asymmetry without synostosis; this represents an example of interaction of environment and a genetic predisposition to cause craniosynostosis. See Genomic Databases table.

Two common mutations account for 98% of Apert syndrome: p.Pro253Arg and p.Ser252Trp [Ferreira et al 1999]. These mutations occur in the identical location as the *FGFR1* mutation in Pfeiffer syndrome and the *FGFR3* mutation in Muenke syndrome. This is the linker region between Ig-like loops II and III, the area thought to be critical in ligand binding; the replacement of a proline for a bulkier arginine may alter the orientation of the IgII and IgIII loops [Wilkie 1997]. The p.Ser252Trp mutation is more common than the p.Pro253Arg mutation, seen in 71% and 26% of individuals with Apert syndrome, respectively. Both mutations augment receptor binding affinity; however, indiscriminate increased affinity of fibroblast growth factor receptor 2 (FGFR2) for any FGF is seen in p.Pro253Arg mutations, whereas p.Ser252Trp mutations convey a selective FGFR2 affinity for a limited subset of FGFs [Ferreira et al 1999].

Rare unique mutations involving Alu element *de novo* insertions have provided evidence that syndactyly in Apert syndrome is caused by signaling through keratinocyte growth factor receptors (KGFRs) [Oldridge et al 1999].

Six *FGFR2* mutations have been identified in individuals with Jackson-Weiss syndrome [Heike et al 2001]. Mutations seen in individuals with Crouzon, Pfeiffer, and Jackson-Weiss syndromes occur in and around the B exon of the third Ig-like domain in *FGFR2*. The exon is subjected to alternative splicing; it is included in the bone *FGFR2* isoform that is expressed in the cranial sutures and limbs, and is spliced out in making the KGFR. Mutations in and around the splice sites cause aberrant splicing [Meyers et al 1996]. Other mutations cause a loss or gain of a cysteine residue, while others alter splice sites [Wilkie 1997]. Identical mutations have been seen in individuals with Crouzon, Pfeiffer, and Jackson-Weiss syndromes [Hollway

et al 1997, Oldridge et al 1997], suggesting that unlinked modifier genes or epigenetic factors play a role in determining the final phenotype. A study of individuals with Crouzon and Pfeiffer syndromes found that 60% of mutations are caused by two mutation hot spots at the critical cysteine residues 278 and 342 [Kress et al 2000].

It is noteworthy that the *FGFR2* mutation appears to arise exclusively from the male chromosome [Moloney et al 1996]. The mutation may convey an advantage in sperm, as the FGF/FGFR pathway is known to be important in maintaining and initiating spermatogenesis [Van Dissel-Emiliani et al 1996]. The *de novo* mutation rate is high, with 11 of 21 cases of Crouzon syndrome and Pfeiffer syndrome found to arise from *de novoFGFR2* mutations [Kress et al 2000].

A mouse model of a gain-of-function mutation in *Fgfr2c* (p.Cys342Tyr) equivalent to a mutation in human Crouzon and Pfeiffer syndromes was shown to recapitulate the phenotype of these disorders. Specific features seen in heterozygotes included shortened face, protruding eyes, and premature fusion of cranial sutures, while homozygotes displayed multiple joint fusions, cleft palate, and defects of the trachea and lung, and died shortly after birth. The study suggests that the long-term aspects of the mutant phenotype, including craniosynostosis, are related to the FGFR2 regulation of the osteoblast lineage [Eswarakumar et al 2004].

Normal gene product: Basic FGFR1 has three extracellular Ig-like domains, a transmembrane domain, and a split tyrosine kinase intracellular domain. The Ig-like domains function in promiscuous ligand binding: any FGFR binds any FGF. With ligand binding, two FGFRs dimerize and activate the tyrosine kinase, initiating an intracellular cascade. Basic FGFR1 and FGFR2 mRNA is found during embryogenesis in cartilage and bone precursors that will form the craniofacial and apical skeleton. In the apical skeleton, basic FGFR1 is expressed throughout the entire developing limb bud, while FGFR2 is primarily expressed in the outer ectodermal layer.

Abnormal gene product: Like the mutations seen in *FGFR1* and *FGFR3,FGFR2* mutations are dominant, so that the effect of the altered protein is seen even in the presence of the normal second allele. Based on a number of studies on fibroblasts and animal models containing *FGFR* mutations, the effect seems to be one of excess activity; i.e., the mutant receptors work better than the wild-type receptors (summarized in Wilkie 1997). For example, one study suggested that mutations causing Apert syndrome increase ligand affinity [Anderson et al 1998] The increased affinity of the receptor for the ligand causes excessive activity, which may then promote excessive receptor down-regulation (summarized in Wilkie 2005).

Mutations of exons IIIa and IIIc, the exons in *FGFR2* that are most commonly associated with Pfeiffer syndrome, frequently involve cysteine codons [Cornejo-Roldan et al 1999]. The loss or gain of the cysteine residues around the IgIII loop, as is commonly seen in Crouzon syndrome, may alter the configuration of the IgIII loop (cysteine-cysteine disulfide bonding is thought to stabilize the IgIII loop). A free unpaired cysteine may enable ligand-free dimerization and activation of the receptor. Similarly, other mutations that alter splice sites may alter ligand binding affinity or allow for ligand-free activation [Wilkie 2005].

***FGFR3*—Normal allelic variants:** *FGFR3* has a genomic size of approximately 15 kb. There are two mRNA splice variants, of which the full nature is unknown. Isoform 1 contains 17 exons and has the largest mRNA product.

Pathologic allelic variants: Mutations in *FGFR3* cause achondroplasia, hypochondroplasia, and thanatophoric dysplasia. An alanine-to-glutamic acid change at amino acid 391 (p.Ala391Glu) was identified in individuals with Crouzon syndrome with acanthosis nigricans

(AN) [Mulliken et al 1999]. In addition, a single mutation, p.Pro250Arg, was identified in a series of individuals and families with craniosynostosis (including some who had been previously diagnosed as having Pfeiffer, Jackson-Weiss, and Saethre-Chotzen syndromes) as well as in the original family with Adelaide-type craniosynostosis (now called Muenke syndrome). A p.Pro250Arg mutation in *FGFR3* was reported in an individual with a mild presentation of Beare-Stevenson syndrome and epidermal hyperplasia [Roscioli et al 2001]. The same mutation had been described in *FGFR2* (Apert syndrome) and *FGFR1* (Pfeiffer syndrome) [Bellus et al 1996, Muenke et al 1997]. See Genomic Databases table.

Normal gene product: Fibroblast growth factor receptor 3 (FGFR3) mRNA is found in highest amounts in the developing central nervous system, but is also present in resting cartilage and the skeletal precursors for all bones during the period of endochondral ossification, but not in hypertrophic cartilage. Normal FGFR3 product has two isoforms as a result of alternative splicing of the third *FGFR2*-like loop; FGFR3 IIIa is found in the brain; FGFR3 IIIb is not.

Abnormal gene product: Like the mutations seen in *FGFR1* and *FGFR2,FGFR3* mutations are dominant, so that the effect of the altered protein is seen even in the presence of the normal second allele. Based on a number of studies on fibroblasts and animal models containing *FGFR* mutations, the effect seems to be one of excess activity; i.e., the mutant receptors work better than the wild type (summarized in Wilkie 2005).

The p.Pro252Arg mutation seen in Muenke syndrome occurs in the region between the second and third Ig-like loops, a site that is thought to be important in ligand binding. The substitution of the bulkier residue is thought to change the configuration of the site, thereby altering ligand binding. The increased affinity of the receptor for ligand causes excessive activity, which may then promote excessive receptor down-regulation (summarized in Wilkie 2005).

No studies have been done on the p.Ala391Glu mutation seen in Crouzon syndrome with AN, but much work has been done on the nearby p.Gly380Arg mutation seen in achondroplasia. The mutation demonstrates weak ligand-free activation. While it seems plausible that the p.Ala391Glu mutation works in the same way, the widely different phenotypes produced by the two mutations suggest that other mechanisms of action may be at work (summarized in Wilkie 2005, Chen & Deng 2005).

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select*  *for the most up-to-date Resources information.*—ED.

AboutFace International
123 Edward Street Suite 1003
Toronto M5G 1E2
Canada
Phone: 800-665-FACE (800-665-3223)
Fax: 416-597-8494
Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

American Cleft Palate-Craniofacial Association
Cleft Palate Foundation
1504 East Franklin Street Suite 102

Chapel Hill NC 27514-2820
Phone: 800-242-5338; 919-933-9044
Fax: 919-933-9604
Email: info@cleftline.org
www.cleftline.org

Children's Craniofacial Association
13140 Coit Road Suite 517
Dallas TX 75240
Phone: 800-535-3643; 214-570-9099
Fax: 214-570-8811
Email: contactCCA@ccakids.com
www.ccakids.com

Let's Face It
University of Michigan
School of Dentistry Dentistry Library
1011 N. University
Ann Arbor, MI 48109-1078
Email: faceit@umich.edu
www.faceit.org

National Institute of Neurological Disorders and Stroke
Craniosynostosis Information Page

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Adachi M, Asakura Y, Matsuo M, Yamamoto T, Hanaki K, Arlt W. POR R457H is a global founder mutation causing Antley-Bixler syndrome with autosomal recessive trait. Am J Med Genet A. 2006;140:633–5. [PubMed: 16470797]

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: 16465081]

Anderson J, Burns HD, Enriquez-Harris P, Wilkie AOM, Heath JK. Apert syndrome mutations in fibroblast growth factor receptor 2 exhibit increased affinity for FGF ligand. Hum Mol Genet. 1998;7:1475–83. [PubMed: 9700203]

Anderson PJ, Netherway DJ, Cox TC, Roscioli T, David DJ. Do Craniosynostosis syndrome phenotypes with both FGFR2 and TWIST mutations have a worse clinical outcome? J Craniofac Surg. 2006;17:166–72. [PubMed: 16432427]

Baroni T, Carinci P, Lilli C, Bellucci C, Aisa MC, Scapoli L, Volinia S, Carinci F, Pezzetti F, Calvitti M, Farina A, Conte C, Bodo M. P253R fibroblast growth factor receptor-2 mutation induces RUNX2 transcript variants and calvarial osteoblast differentiation. J Cell Physiol. 2005;202:524–35. [PubMed: 15389579]

Bellus GA, Gaudenz K, Zackai EH, Clarke LA, Szabo J, Francomano CA, Muenke M. Identical mutations in three different fibroblast growth factor receptor genes in autosomal dominant craniosynostosis syndromes. Nat Genet. 1996;14:174–6. [PubMed: 8841188]

Benacerraf BR, Spiro R, Mitchell AG. Using three-dimensional ultrasound to detect craniosynostosis in a fetus with Pfeiffer syndrome. Ultrasound Obstet Gynecol. 2000;16:391–4. [PubMed: 11169319]

Biesecker LG. Strike three for GLI3. Nat Genet. 1997;17:259–60. [PubMed: 9354780]

Binaghi S, Gudinchet F, Rilliet B. Three-dimensional spiral CT of craniofacial malformations in children. Pediatr Radiol. 2000;30:856–60. [PubMed: 11149095]

Bottero L, Cinalli G, Labrune P, Lajeunie E, Marchac D, Renier D. [Antley-Bixler syndrome. Description of two new cases and review of the literature. Prognostic and therapeutic aspects] Ann Chir Plast Esthet. 1997;42:48–55. [PubMed: 9768136]

Chen L, Deng CX. Roles of FGF signaling in skeletal development and human genetic diseases. Front Biosci. 2005;10:1961–76. [PubMed: 15769677]

Chinen Y, Kaname T, Yanagi K, Saito N, Naritomi K, Ohta T. Opitz trigonocephaly C syndrome in a boy with a de novo balanced reciprocal translocation t(3;18)(q13.13;q12.1). Am J Med Genet A. 2006;140:1655–7. [PubMed: 16835930]

Chun K, Teebi AS, Azimi C, Steele L, Ray PN. Screening of patients with craniosynostosis: molecular strategy. Am J Med Genet A. 2003;120:470–3. [PubMed: 12884424]

Cohen MM Jr. A matter of reading English [letter; comment]. Am J Med Genet. 1996;63:503–4. [PubMed: 8737661]

Cohen MM Jr. Pfeiffer syndrome update, clinical subtypes, and guidelines for differential diagnosis. Am J Med Genet. 1993;45:300–7. [PubMed: 8434615]

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

Colvin JS, Bohne BA, Harding GW, McEwen DG, Ornitz DM. Skeletal overgrowth and deafness in mice lacking fibroblast growth factor receptor 3. Nat Genet. 1996;12:390–7. [PubMed: 8630492]

Cornejo-Roldan LR, Roessler E, Muenke M. Analysis of the mutational spectrum of the FGFR2 gene in Pfeiffer syndrome. Hum Genet. 1999;104:425–31. [PubMed: 10394936]

Coumoul X, Deng CX. Roles of FGF receptors in mammalian development and congenital diseases. Birth Defects Res C Embryo Today. 2003;69:286–304. [PubMed: 14745970]

de Ravel TJ, Taylor IB, Van Oostveldt AJ, Fryns JP, Wilkie AO. A further mutation of the FGFR2 tyrosine kinase domain in mild Crouzon syndrome. Eur J Hum Genet. 2005;13:503–5. [PubMed: 15523492]

Deng C, Wynshaw-Boris A, Zhou F, Kuo A, Leder P. Fibroblast growth factor receptor 3 is a negative regulator of bone growth. Cell. 1996;84:911–21. [PubMed: 8601314]

Eswarakumar VP, Horowitz MC, Locklin R, Morriss-Kay GM, Lonai P. A gain-of-function mutation of Fgfr2c demonstrates the roles of this receptor variant in osteogenesis. Proc Natl Acad Sci U S A. 2004;101:12555–60. [PubMed: 15316116]

Farrow EG, Davis SI, Mooney SD, Beighton P, Mascarenhas L, Gutierrez YR, Pitukcheewanont P, White KE. Extended mutational analyses of FGFR1 in osteoglophonic dysplasia. Am J Med Genet A. 2006;140:537–9. [PubMed: 16470795]

Ferreira JC, Carter SM, Bernstein PS, Jabs EW, Glickstein JS, Marion RW, Baergen RN, Gross SJ. Second-trimester molecular prenatal diagnosis of sporadic Apert syndrome following suspicious ultrasound findings. Ultrasound Obstet Gynecol. 1999;14:426–30. [PubMed: 10658283]

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: 16526917]

Gaudenz K, Roessler E, Vainikka S, Alitalo K, Muenke M. Analysis of patients with craniosynostosis syndromes for a pro246Arg mutation of FGFR4. Mol Genet Metab. 1998;64:76–79. [PubMed: 9682222]

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: 10712195]

Gonzales M, Heuertz S, Martinovic J, Delahaye S, Bazin A, Loget P, Pasquier L, Le Merrer M, Bonaventure J. Vertebral anomalies and cartilaginous tracheal sleeve in three patients with Pfeiffer

syndrome carrying the S351C FGFR2 mutation. Clin Genet. 2005;68:179–81. [PubMed: 15996217]

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: 12893942]

Gripp KW, McDonald-McGinn DM, Gaudenz K, Whitaker LA, Bartlett SP, Glat PM, Cassileth LB, Mayro R, Zackai EH, Muenke M. Identification of a genetic cause for isolated unilateral coronal synostosis: a unique mutation in the fibroblast growth factor receptor 3. J Pediatr. 1998;132:714–6. [PubMed: 9580776]

Grosso S, Farnetani MA, Berardi R, Bartalini G, Carpentieri M, Galluzzi P, Mostardini R, Morgese G, Balestri P. Medial temporal lobe dysgenesis in Muenke syndrome and hypochondroplasia. Am J Med Genet A. 2003;120:88–91. [PubMed: 12794698]

Hackett A, Rowe L. FGFR1 Pfeiffer syndrome without craniosynostosis: an additional case report. Clin Dysmorphol. 2006;15:207–10. [PubMed: 16957473]

Hansen WF, Rijhsinghani A, Grant S, Yankowitz J. Prenatal diagnosis of Apert syndrome. Fetal Diagn Ther. 2004;19:127–30. [PubMed: 14764955]

Hatch NE, Hudson M, Seto ML, Cunningham ML, Bothwell M. Intracellular retention, degradation, and signaling of glycosylation-deficient FGFR2 and craniosynostosis syndrome-associated FGFR2C278F. J Biol Chem. 2006;281:27292–305. [PubMed: 16844695]

Heike C, Seto M, Hing A, Palidin A, Hu FZ, Preston RA, Ehrlich GD, Cunningham M. Century of Jackson-Weiss syndrome: further definition of clinical and radiographic findings in "lost" descendants of the original kindred. Am J Med Genet. 2001;100:315–24. [PubMed: 11343323]

Hockstein NG, McDonald-McGinn D, Zackai E, Bartlett S, Huff DS, Jacobs IN. Tracheal anomalies in Pfeiffer syndrome. Arch Otolaryngol Head Neck Surg. 2004;130:1298–302. [PubMed: 15545585]

Hollway GE, Suthers GK, Haan EA, Thompson E, David DJ, Gecz J, Mulley JC. Mutation detection in FGFR2 craniosynostosis syndromes. Hum Genet. 1997;99:251–5. [PubMed: 9048930]

Hunt CE, Puczynski MS. Does supine sleeping cause asymmetric heads? Pediatrics. 1996;98:127–9. [PubMed: 8668385]

Ibrahimi OA, Zhang F, Eliseenkova AV, Linhardt RJ, Mohammadi M. Proline to arginine mutations in FGF receptors 1 and 3 result in Pfeiffer and Muenke craniosynostosis syndromes through enhancement of FGF binding affinity. Hum Mol Genet. 2004;13:69–78. [PubMed: 14613973]

Ignelzi MA Jr, Wang W, Young AT. Fibroblast growth factors lead to increased Msx2 expression and fusion in calvarial sutures. J Bone Miner Res. 2003;18:751–9. [PubMed: 12674336]

Ito S, Sekido K, Kanno H, Sato H, Tanaka M, Yamaguchi K, Yamamoto I. Phenotypic diversity in patients with craniosynostoses unrelated to Apert syndrome: the role of fibroblast growth factor receptor gene mutations. J Neurosurg. 2005;102:23–30. [PubMed: 16206730]

Itoh S, Nojima M, Yoshida K. Usefulness of magnetic resonance imaging for accurate diagnosis of Pfeiffer syndrome type II in utero. Fetal Diagn Ther. 2006;21:168–71. [PubMed: 16490997]

Jadico SK, Young DA, Huebner A, Edmond JC, Pollock AN, McDonald-McGinn DM, Li YJ, Zackai EH, Young TL. Ocular abnormalities in Apert syndrome: genotype/phenotype correlations with fibroblast growth factor receptor type 2 mutations. J AAPOS. 2006;10:521–7. [PubMed: 17189145]

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: 16526918]

Jenkins D, Seelow D, Jehee FS, Perlyn CA, Alonso LG, Bueno DF, Donnai D, Josifiova D, Mathijssen IM, Morton JE, Orstavik KH, Sweeney E, Wall SA, Marsh JL, Nurnberg P, Passos-Bueno MR, Wilkie AO. RAB23 mutations in Carpenter syndrome imply an unexpected role for hedgehog signaling in cranial-suture development and obesity. Am J Hum Genet. 2007;80:1162–70. [PubMed: 17503333]

Kanauchi Y, Muragaki Y, Ogino T, Takahara M, Tsuchida H, Ishigaki D. FGFR2 mutation in a patient with Apert syndrome associated with humeroradial synostosis. Congenit Anom (Kyoto). 2003;43:302–5. [PubMed: 15041782]

Kane AA, Mitchell LE, Craven KP, Marsh JL. Observations on a recent increase in plagiocephaly without synostosis. Pediatrics. 1996;97:877–85. [PubMed: 8657530]

Kim BG, Kim HJ, Park HJ, Kim YJ, Yoon WJ, Lee SJ, Ryoo HM, Cho JY. Runx2 phosphorylation induced by fibroblast growth factor-2/protein kinase C pathways. Proteomics. 2006;6:1166–74. [PubMed: 16421932]

Kress W, Collmann H, Busse M, Halliger-Keller B, Mueller CR. Clustering of FGFR2 gene mutations inpatients with Pfeiffer and Crouzon syndromes (FGFR2-associated craniosynostoses). Cytogenet Cell Genet. 2000;91:134–7. [PubMed: 11173845]

Kress W, Schropp C, Lieb G, Petersen B, Busse-Ratzka M, Kunz J, Reinhart E, Schafer WD, Sold J, Hoppe F, Pahnke J, Trusen A, Sorensen N, Krauss J, Collmann H. Saethre-Chotzen syndrome caused by TWIST 1 gene mutations: functional differentiation from Muenke coronal synostosis syndrome. Eur J Hum Genet. 2006;14:39–48. [PubMed: 16251895]

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: 10067911]

Lajeunie E, Heuertz S, El Ghouzzi V, Martinovic J, Renier D, Le Merrer M, Bonaventure J. Mutation screening in patients with syndromic craniosynostoses indicates that a limited number of recurrent FGFR2 mutations accounts for severe forms of Pfeiffer syndrome. Eur J Hum Genet. 2006;14:289–98. [PubMed: 16418739]

Lajeunie E, Le Merrer M, Bonaiti-Pellie C, Marchac D, Renier D. Genetic study of scaphocephaly. Am J Med Genet. 1996;62:282–5. [PubMed: 8882788]

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: 15602758]

Mahieu-Caputo D, Sonigo P, Amiel J, Simon I, Aubry MC, Lemerrer M, Delezoide AL, Gigarel N, Dommergues M, Dumez Y. Prenatal diagnosis of sporadic Apert syndrome: a sequential diagnostic approach combining three-dimensional computed tomography and molecular biology. Fetal Diagn Ther. 2001;16:10–2. [PubMed: 11125244]

Marohnic CC, Panda SP, Martasek P, Masters BS. Diminished FAD binding in the Y459H and V492E Antley-Bixler syndrome mutants of human cytochrome P450 reductase. J Biol Chem. 2006;281:35975–82. [PubMed: 16998238]

Matsumoto K, Nakanishi H, Kubo Y, Yokozeki M, Moriyama K. Advances in distraction techniques for craniofacial surgery. J Med Invest. 2003;50:117–25. [PubMed: 13678380]

McGillivray G, Savarirayan R, Cox TC, Stojkoski C, McNeil R, Bankier A, Bateman JF, Roscioli T, Gardner RJ, Lamande SR. Familial scaphocephaly syndrome caused by a novel mutation in the FGFR2 tyrosine kinase domain. J Med Genet. 2005;42:656–62. [PubMed: 16061565]

Meyers GA, Day D, Goldberg R, Daentl DL, Przylepa KA, Abrams LJ, Graham JM Jr, Feingold M, Moeschler JB, Rawnsley E, Scott AF, Jabs EW. FGFR2 exon IIIa and IIIc mutations in Crouzon, Jackson-Weiss, and Pfeiffer syndromes: evidence for missense changes, insertions, and a deletion due to alternative RNA splicing. Am J Hum Genet. 1996;58:491–8. [PubMed: 8644708]

Moloney DM, Slaney SF, Oldridge M, Wall SA, Sahlin P, Stenman G, Wilkie AO. Exclusive paternal origin of new mutations in Apert syndrome [see comments]. Nat Genet. 1996;13:48–53. [PubMed: 8673103]

Muenke M, Schell U. Fibroblast-growth-factor receptor mutations in human skeletal disorders. Trends Genet. 1995;11:308–13. [PubMed: 8585128]

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, et al. 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: 9042914]

Mulliken JB, Gripp KW, Stolle CA, Steinberger D, Muller U. Molecular analysis of patients with synostotic frontal plagiocephaly (unilateral coronal synostosis). Plast Reconstr Surg. 2004;113:1899–909. [PubMed: 15253176]

Mulliken JB, Steinberger D, Kunze S, Muller U. Molecular diagnosis of bilateral coronal synostosis. Plast Reconstr Surg. 1999;104:1603–15. [PubMed: 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;73:61–66. [PubMed: 9375924]

Oldridge M, Lunt PW, Zackai EH, McDonald-McGinn DM, Muenke M, Moloney DM, Twigg SR, Heath JK, Howard TD, Hoganson G, Gagnon DM, Jabs EW, Wilkie AO. Genotype-phenotype correlation for nucleotide substitutions in the IgII- IgIII linker of FGFR2. Hum Mol Genet. 1997;6:137–43. [PubMed: 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: 9973282]

Oliveira NA, Alonso LG, Fanganiello RD, Passos-Bueno MR. Further evidence of association between mutations in FGFR2 and syndromic craniosynostosis with sacrococcygeal eversion. Birth Defects Res A Clin Mol Teratol. 2006;76:629–33. [PubMed: 16955501]

Ornitz DM. FGF signaling in the developing endochondral skeleton. Cytokine Growth Factor Rev. 2005;16:205–13. [PubMed: 15863035]

Posnick JC, Ruiz RL. The craniofacial dysostosis syndromes: current surgical thinking and future directions. Cleft Palate Craniofac J. 2000;37:433. [PubMed: 11034022]

Przylepa KA, Paznekas W, Zhang M, Golabi M, Bias W, Bamshad MJ, Carey JC, Hall BD, Stevenson R, Orlow S, Cohen MM Jr, Jabs EW. Fibroblast growth factor receptor 2 mutations in Beare-Stevenson cutis gyrata syndrome. Nat Genet. 1996;13:492–4. [PubMed: 8696350]

Quintero-Rivera F, Robson CD, Reiss RE, Levine D, Benson C, Mulliken JB, Kimonis VE. Apert syndrome: what prenatal radiographic findings should prompt its consideration? Prenat Diagn. 2006;26:966–72. [PubMed: 16906598]

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: 15241680]

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: 8683284]

Renier D, El-Ghouzzi V, Bonaventure J, Le Merrer M, Lajeunie E. Fibroblast growth factor receptor 3 mutation in nonsyndromic coronal synostosis: clinical spectrum, prevalence, and surgical outcome. J Neurosurg. 2000;92:631–6. [PubMed: 10761652]

Renier D, Lajeunie E, Arnaud E, Marchac D. Management of craniosynostoses. Childs Nerv Syst. 2000;16:645–58. [PubMed: 11151714]

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: 8882401]

Roscioli T, Flanagan S, Mortimore RJ, Kumar P, Weedon D, Masel J, Lewandowski R, Hyland V, Glass IA. Premature calvarial synostosis and epidermal hyperplasia (Beare- Stevenson syndrome-like anomalies) resulting from a P250R missense mutation in the gene encoding fibroblast growth factor receptor 3. Am J Med Genet. 2001;101:187–94. [PubMed: 11424131]

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: 14564217]

Saavedra D, Richieri-Costa A, Guion-Almeida ML, Cohen MM Jr. Craniofrontonasal syndrome: study of 41 patients. Am J Med Genet. 1996;61:147–51. [PubMed: 8669441]

Schweitzer DN, Graham JM Jr, Lachman RS, Jabs EW, Okajima K, Przylepa KA, Shanske A, Chen K, Neidich JA, Wilcox WR. Subtle radiographic findings of achondroplasia in patients with Crouzon syndrome with acanthosis nigricans due to an Ala391Glu substitution in FGFR3. Am J Med Genet. 2001;98:75–91. [PubMed: 11426459]

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

Steinberger D, Collmann H, Schmalenberger B, Muller U. A novel mutation (a886g) in exon 5 of FGFR2 in members of a family with Crouzon phenotype and plagiocephaly. J Med Genet. 1997;34:420–2. [PubMed: 9152842]

Steinberger D, Reinhartz T, Unsold R, Muller U. FGFR2 mutation in clinically nonclassifiable autosomal dominant craniosynostosis with pronounced phenotypic variation. Am J Med Genet. 1996;66:81–86. [PubMed: 8957519]

Stevens CA, Roeder ER. Ser351Cys mutation in the fibroblast growth factor receptor 2 gene results in severe Pfeiffer syndrome. Clin Dysmorphol. 2006;15:187–8. [PubMed: 16760743]

Tartaglia M, Bordoni V, Velardi F, Basile RT, Saulle E, Tenconi R, Di Rocco C, Battaglia PA. Fibroblast growth factor receptor mutational screening in newborns affected by metopic synostosis. Childs Nerv Syst. 1999;15:389–93. [PubMed: 10447608]

Tholpady SS, Abdelaal MM, Dufresne CR, Gampper TJ, Lin KY, Jane JA Sr, Morgan RF, Ogle RC. Aberrant bony vasculature associated with activating fibroblast growth factor receptor mutations accompanying Crouzon syndrome. J Craniofac Surg. 2004;15:431–5. [PubMed: 15111803]

Thomas GP, Wilkie AO, Richards PG, Wall SA. FGFR3 P250R mutation increases the risk of reoperation in apparent 'nonsyndromic' coronal craniosynostosis. J Craniofac Surg. 2005;16:347–52. [PubMed: 15915095]

Toydemir RM, Brassington AE, Bayrak-Toydemir P, Krakowiak PA, Jorde LB, Whitby FG, Longo N, Viskochil DH, Carey JC, Bamshad MJ. A novel mutation in FGFR3 causes camptodactyly, tall stature, and hearing loss (CATSHL) syndrome. Am J Hum Genet. 2006;79:935–41. [PubMed: 17033969]

Van Dissel-Emiliani FM, De Boer-Brouwer M, De Rooij DG. Effect of fibroblast growth factor-2 on Sertoli cells and gonocytes in coculture during the perinatal period. Endocrinology. 1996;137:647–54. [PubMed: 8593814]

Van Maldergem L, Siitonen HA, Jalkh N, Chouery E, De Roy M, Delague V, Muenke M, Jabs EW, Cai J, Wang LL, Plon SE, Fourneau C, Kestila M, Gillerot Y, Megarbane A, Verloes A. Revisiting the craniosynostosis-radial ray hypoplasia association: Baller-Gerold syndrome caused by mutations in the RECQL4 gene. J Med Genet. 2006;43:148–52. [PubMed: 15964893]

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: 10735635]

Warman ML, Mulliken JB, Hayward PG, Muller U. Newly recognized autosomal dominant disorder with craniosynostosis. Am J Med Genet. 1993;46:444–9. [PubMed: 8357019]

White KE, Cabral JM, Davis SI, Fishburn T, Evans WE, Ichikawa S, Fields J, Yu X, Shaw NJ, McLellan NJ, McKeown C, Fitzpatrick D, Yu K, Ornitz DM, Econs MJ. Mutations that cause osteoglophonic dysplasia define novel roles for FGFR1 in bone elongation. Am J Hum Genet. 2005;76:361–7. [PubMed: 15625620]

Wilkie AO. Craniosynostosis: genes and mechanisms. Hum Mol Genet. 1997;6:1647–56. [PubMed: 9300656]

Wilkie AO. Bad bones, absent smell, selfish testes: the pleiotropic consequences of human FGF receptor mutations. Cytokine Growth Factor Rev. 2005;16:187–203. [PubMed: 15863034]

Wilkie AO, Oldridge M, Tang Z, Maxson RE Jr. Craniosynostosis and related limb anomalies. Novartis Found Symp. 2001;232:122–33. [PubMed: 11277076]

Wilkie AOM, Mavrogiannis LA. Enlarged Parietal Foramina/Cranium Bifidum. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2005. Available at http://www.genetests.org. Updated 2004

Williamson L, Arlt W, Shackleton C, Kelley RI, Braddock SR. Linking Antley-Bixler syndrome and congenital adrenal hyperplasia: a novel case of P450 oxidoreductase deficiency. Am J Med Genet A. 2006;140:1797–803. [PubMed: 16906539]

Wong GB, Kakulis EG, Mulliken JB. Analysis of fronto-orbital advancement for Apert, Crouzon, Pfeiffer, and Saethre-Chotzen syndromes. Plast Reconstr Surg. 2000;105:2314–23. [PubMed: 10845283]

Zackai EH, McDonald-McGinn DM, Stolle C, Huff DS. Craniosynostosis with tracheal sleeve: a patient with Pfeiffer syndrome, tracheal sleeve and additional malformations in whom an FGFR2 mutation was found. Clin Dysmorphol. 2003;12:209. [PubMed: 14564165]

Suggested Readings

Ades LC, Mulley JC, Senga IP, Morris LL, David DJ, Haan EA. Jackson-Weiss syndrome: clinical and radiological findings in a large kindred and exclusion of the gene from 7p21 and 5qter. Am J Med Genet. 1994;51:121–30. [PubMed: 8092187]

American Cleft Palate-Craniofacial Association. Parameters for evaluation and treatment of patients with cleft lip/palate or other craniofacial anomalies. Cleft Palate Craniofac J 30 [suppl]:S1-16. 1993 [PubMed: 8457579]

Cohen MM Jr. Craniosynostoses: phenotypic/molecular correlations [editorial] [see comments]. Am J Med Genet. 1995;56:334–9. [PubMed: 7778605]

Cohen MM Jr. Lambdoid synostosis is an overdiagnosed condition [letter]. Am J Med Genet. 1996;61:98–99. [PubMed: 8741932]

Cohen MM Jr. An etiologic and nosologic overview of craniosynostosis syndromes. Birth Defects Orig Art Ser XI(2):137-89. 1973

Cohen MM Jr. Cloverleaf syndrome update. Proc Green Genet Ctr. 1973;6:186–7.

Cohen MM Jr, Kreiborg S. Birth prevalence studies of the Crouzon syndrome: comparison of direct and indirect methods. Clin Genet. 1992;41:12–15. [PubMed: 1633640]

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

Czeizel AE, Elek C, Susanszky E. Birth prevalence study of the Apert syndrome [letter; comment]. Am J Med Genet. 1993;45:392–3. [PubMed: 8434630]

el Ghouzzi V, Le Merrer M, Perrin-Schmitt F, Lajeunie E, Benit P, Renier D, Bourgeois P, Bolcato-Bellemin AL, Munnich A, Bonaventure J. Mutations of the TWIST gene in the Saethre-Chotzen syndrome [see comments]. Nat Genet. 1997;15:42–46. [PubMed: 8988167]

Howard TD, Paznekas WA, Green ED, Chiang LC, Ma N, Ortiz de Luna RI, Garcia Delgado C, Gonzalez-Ramos M, Kline AD, Jabs EW. Mutations in TWIST, a basic helix-loop-helix transcription factor, in Saethre-Chotzen syndrome. Nat Genet. 1997;15:36–41. [PubMed: 8988166]

Ma HW, Lajeunie E, Le Merrer M, de Parseval N, Serville F, Weissenbach J, Munnich A, Renier D. No evidence of genetic heterogeneity in Crouzon craniofacial dysostosis. Hum Genet. 1995;96:731–5. [PubMed: 8522336]

Ma L, Golden S, Wu L, Maxson R. The molecular basis of Boston-type craniosynostosis: the Pro148-->His mutation in the N-terminal arm of the MSX2 homeodomain stabilizes DNA binding without altering nucleotide sequence preferences. Hum Mol Genet. 1996;5:1915–20. [PubMed: 8968743]

McCarthy JG, Glasberg SB, Cutting CB, Epstein FJ, Grayson BH, Ruff G, Thorne CH, Wisoff J, Zide BM. Twenty-year experience with early surgery for Craniosynostosis: II. The craniofacial synostosis syndromes and pansynostosis - results and unsolved problems. Plast Reconstr Surg. 1995;96:284–98. [PubMed: 7624401]

Moore MH, Cantrell SB, Trott JA, David DJ. Pfeiffer syndrome: a clinical review. Cleft Palate Craniofac J. 1995;32:62–70. [PubMed: 7727489]

Muenke M, Wilkie AOM. Craniosynostosis Syndromes. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B (eds) The Metabolic and Molecular Bases of Inherited Disease (OMMBID), McGraw-Hill, New York, Chap 245. www.ommbid.com. revised 2002

Muenke M, Schell U, Robin NH, et al. Variable clinical spectrum in Pfeiffer syndrome: correlation between phenotype and genotype. Proc Green Genet Ctr. 1995;15:126.

Park WJ, Meyers GA, Li X, Theda C, Day D, Orlow SJ, Jones MC, Jabs EW. Novel FGFR2 mutations in Crouzon and Jackson-Weiss syndromes show allelic heterogeneity and phenotypic variability. Hum Mol Genet. 1995;4:1229–33. [PubMed: 8528214]

Robin NH, Scott JA, Arnold JE, Goldstein JA, Shilling BB, Marion RW, Cohen MM Jr. Favorable prognosis for children with Pfeiffer syndrome types 2 and 3: implications for classification. Am J Med Genet. 1998;75:240–4. [PubMed: 9475589]

Steinberger D, Mulliken JB, Muller U. Predisposition for cysteine substitutions in the immunoglobulin-like chain of FGFR2 in Crouzon syndrome. Hum Genet. 1995;96:113–5. [PubMed: 7607643]

Tartaglia M, Di Rocco C, Lajeunie E, Valeri S, Velardi F, Battaglia PA. Jackson-Weiss syndrome: identification of two novel FGFR2 missense mutations shared with Crouzon and Pfeiffer craniosynostotic disorders. Hum Genet. 1997;101:47–50. [PubMed: 9385368]

Winter RM, Reardon W. Lumpers, splitters, and FGFRs [letter; comment]. Am J Med Genet. 1996;63:501–2. [PubMed: 8737660]

Chapter Notes

Revision History

- 27 September 2007 (me) Comprehensive update posted to live Web site
- 9 January 2006 (nr) Revision: Table 3, Pfeiffer syndrome
- 18 April 2005 (me) Comprehensive update posted to live Web site
- 13 February 2003 (me) Comprehensive update posted to live Web site
- 20 October 1998 (pb) Review posted to live Web site
- March 1998 (nr) Original submission