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Muenke Syndrome

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Summary

Clinical characteristics

Muenke syndrome is characterized by considerable phenotypic variability; features may include coronal synostosis (more often bilateral than unilateral); synostosis of other sutures, all sutures (pan synostosis), or no sutures; or macrocephaly. Bilateral coronal synostosis typically results in brachycephaly, although turribrachycephaly (a "tower-shaped" skull) or a cloverleaf skull can be observed. Unilateral coronal synostosis results in anterior plagiocephaly. Other craniofacial findings typically include temporal bossing, widely spaced eyes, ptosis or mild proptosis, mild midface retrusion, and highly arched palate or cleft lip and palate. Strabismus is common. Other findings can include hearing loss, developmental delay, intellectual disability, behavioral issues, intracranial anomalies, epilepsy, ocular anomalies, brachydactyly, carpal and/or tarsal bone fusions, broad thumbs and great toes, clinodactyly, and radiographic findings of short and broad middle phalanges and/or cone-shaped epiphyses. Of note, some individuals who have the p.Pro250Arg pathogenic variant may have no signs of Muenke syndrome on physical or radiographic examination.

Diagnosis/testing

The diagnosis of Muenke syndrome is established by the identification of the *FGFR3* pathogenic variant c.749C>G (p.Pro250Arg) by molecular genetic testing.

Management

Treatment of manifestations: Children with Muenke syndrome and craniosynostosis are best managed by a pediatric craniofacial clinic, which typically includes a craniofacial surgeon and neurosurgeon, clinical geneticist, ophthalmologist, otolaryngologist, pediatrician, radiologist, psychologist, dentist, audiologist, speech therapist, and social worker. Depending on severity, the first craniosynostosis repair (fronto-orbital advancement and cranial vault remodeling) is typically performed between ages three and six months. An alternative approach is endoscopic strip craniectomy, which is a less invasive procedure and is typically performed prior to age three

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months. Postoperative increased intracranial pressure and/or the need for secondary or tertiary extracranial contouring may occur. Standard treatments for hearing loss; early speech therapy and intervention programs for those with developmental delay, intellectual impairment, behavioral issues, and/or hearing loss; surgical correction for strabismus; lubrication for exposure keratopathy.

Surveillance: Affected individuals benefit from integrated multidisciplinary care and protocol-driven management from birth to maturity that includes audiograms to screen for acquired or progressive hearing loss; developmental and behavioral assessments; neurologic assessment for seizures; ophthalmology assessment for strabismus; and social work assessment.

Evaluation of relatives at risk: It is appropriate to evaluate relatives at risk in order to identify as early as possible those who would benefit from institution of treatment and preventive measures.

Genetic counseling

Muenke syndrome is inherited in an autosomal dominant manner. Each child of an individual with Muenke syndrome has a 50% chance of inheriting the pathogenic variant. Because penetrance is reduced and the phenotype is variable within families, the manifestations in a child who inherits the pathogenic variant cannot be predicted based on the phenotypes of other heterozygous family members. Once the *FGFR3* p.Pro250Arg pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for Muenke syndrome are possible.

Diagnosis

Suggestive Findings

Muenke syndrome **should be suspected** in individuals with the following clinical, radiographic, and family history findings. The phenotype is variable and ranges from no detectable clinical manifestations to the presence of craniosynostosis along with other classic features.

Clinical features

- Facial asymmetry
- Brachycephaly, turribrachycephaly (a "tower-shaped" skull), or cloverleaf skull
- Sutural ridging over both (or less commonly one) of the coronal sutures accompanied by:
  - Ipsilaterally: flattening of the forehead, elevation of the superior orbital rim, elevation of the eyebrow, anterior placement of the ear, deviation of the nasal root
  - Contralaterally: frontal bossing of the forehead, depression of the eyebrow
- Temporal bossing
- Macrocephaly without craniosynostosis
- Craniosynostosis with sensorineural hearing loss

Radiographic findings

- Head CT with three-dimensional reconstruction demonstrating:
  - Unilateral coronal craniosynostosis
  - Bilateral coronal craniosynostosis
  - Synostosis of other sutures (lambdoid, metopic, sagittal, squamosal)
- Extracranial radiographic features can include:
  - Fusion of the carpal bones (commonly the capitate and hamate or trapezoid and trapezium bones) [Muenke et al 1997, Trusen et al 2003, Kruszka et al 2016]

- Fusion of the tarsal bones (commonly the calcaneus and cuboid bones) [Muenke et al 1997, Trusen et al 2003, Agochukwu et al 2013, Kruszka et al 2016]
- Thimble-like (short and broad) middle phalanges of the hands and feet [Muenke et al 1997, Kruszka et al 2016]
- Epiphyseal coning [Muenke et al 1997, Kruszka et al 2016]

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of Muenke syndrome **is established** in a proband by the identification of a heterozygous c.749C>G (p.Pro250Arg) pathogenic variant in *FGFR3* by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *FGFR3* can be performed first. Note: Targeted analysis for the p.Pro250Arg pathogenic variant in *FGFR3* is rarely performed because the clinical features of Muenke syndrome overlap with those of other craniosynostosis syndromes caused by different heterozygous pathogenic variants in *FGFR3* and other craniosynostosis-related genes (see Differential Diagnosis).
- **A multigene panel** that includes *FGFR3* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Table 1. Molecular Genetic Testing Used in Muenke Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
FGFR3	Sequence analysis [3]	100% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Muenke syndrome is defined by the specific pathogenic variant c.749C>G (p.Pro250Arg) [Bellus et al 1996].

Clinical Characteristics

Clinical Description

Muenke syndrome is characterized by coronal synostosis, and occasionally synostosis of other sutures, abnormal skull shape in those with synostosis, characteristic facies, hearing loss, and strabismus. Additional features can include developmental delay, intellectual disability, epilepsy, intracranial anomalies, brachydactyly, broad thumbs and great toes, and/or clinodactyly. Penetrance is incomplete, and phenotypic variability is considerable even within the same family. Some individuals have minor clinical signs such as macrocephaly and subtle facial findings without craniosynostosis; some have only radiographic features [Muenke et al 1997]. To date, more than 100 individuals have been identified with a p.Pro250Arg pathogenic variant in *FGFR3* [Kruszka et al 2016]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Muenke Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Coronal synostosis	~85%	
Synostosis of other sutures	~3	
Hearing loss	>70%	
Developmental delay	>60%	
Intellectual disability	>40%	
Behavioral issues	~50%	
Ocular anomalies	>60%	Strabismus in 39%-66%
Limb findings	~50%	

Craniosynostosis and craniofacial features. Coronal synostosis may be bilateral (~2/3 of affected individuals) or unilateral (~1/3 of affected individuals) [Keller et al 2007, Kruszka et al 2016]. Occasionally, other sutures may be involved, including the metopic suture (leading to trigonocephaly), the sagittal suture, the squamosal suture, or – rarely – all sutures (pan synostosis) [van der Meulen et al 2006, Doumit et al 2014, Kruszka et al 2016]. Craniosynostosis is not always present; approximately 12%-15% of individuals heterozygous for the *FGFR3* p.Pro250Arg pathogenic variant had no evidence of craniosynostosis [Renier et al 2000, Kruszka et al 2016].

Bilateral coronal synostosis typically results in brachycephaly, although turribrachycephaly (a "tower-shaped" skull) or a cloverleaf skull can be observed. Unilateral coronal synostosis results in anterior plagiocephaly (asymmetry of the skull and face).

Other craniofacial findings typically include temporal bossing, widely spaced eyes, ptosis or proptosis (usually mild), and midface retrusion (usually mild). Rarer craniofacial features include malar flattening, a short nose with anteverted nares and a depressed nasal bridge, deviation of the nasal septum, an overhanging nasal tip, high-arched palate, cleft lip and/or palate, dental malocclusion, mild retrognathia, hypoplastic auricles, and low-set ears.

Hearing loss. In a large international cohort, more than 70% of individuals with Muenke syndrome had hearing loss, with a majority of individuals with hearing loss having bilateral sensorineural hearing loss (70.8%) and the remainder having conductive (22%) and mixed forms of hearing loss (8.6%). There is evidence that sensorineural hearing loss (usually mild and mid-to-low frequency) is specific to Muenke syndrome compared

to other *FGFR*-related craniosynostosis syndromes [Agochukwu et al 2014a], sometimes occurring in individuals with Muenke syndrome who do not have craniosynostosis [Hollway et al 1998].

Children with Muenke syndrome and craniosynostosis can develop hearing loss following a normal newborn hearing screen [E Doherty & M Muenke, personal observation]. Individuals may have recurrent episodes of otitis media treated with myringotomy tube placement [Didolkar et al 2009, Kruszka et al 2016], which may explain the occurrence of conductive hearing loss in some individuals. Additionally, some individuals may have progressive hearing loss.

Developmental delay and behavioral issues. In a large international study, 40.8% of individuals with Muenke syndrome were reported to have intellectual disability and 66.3% had developmental delay, with speech delay the most common type of developmental delay (61.1%) [Kruszka et al 2016]. Developmental delay and/or intellectual disability is usually mild. Individuals with Muenke syndrome were more likely to be intellectually impaired than individuals with Crouzon syndrome [Flapper et al 2009] and had slightly lower IQ than other individuals with craniosynostosis without the *FGFR3* p.Pro250Arg pathogenic variant [Arnaud et al 2002].

Compared to normative populations, individuals with Muenke syndrome have also been reported to be at increased risk for developing some behavioral and emotional issues [Maliepaard et al 2014]. Bannink et al [2011] found behavioral issues to be more common in boys with Muenke syndrome, with a prevalence of 50%. Approximately 24% of individuals with Muenke syndrome had a diagnosis of attention-deficit/hyperactivity disorder [Kruszka et al 2016].

Individuals with Muenke syndrome were at increased risk for developing adaptive and executive functioning issues [Yarnell et al 2015]. Interestingly, the change in behavior in the affected cohort was not dependent on the presence or absence of craniosynostosis or hearing loss, raising the question of an intrinsic brain effect of the *FGFR3* p.Pro250Arg pathogenic variant that is distinct from the change in skull shape.

Neurologic abnormalities. Differences in patterns of the expression, formation, and structure of the central nervous system may be partly responsible for the developmental delay and intellectual disability observed in Muenke syndrome.

- The following intracranial anomalies have been reported:
  - Hippocampus and bilateral medial temporal dysgenesis in one person [Grosso et al 2003], described as developmentally normal
  - Bilateral lateral ventricular dilatation and a small cerebellum in one person [Yu et al 2010]
  - Porencephalic cyst of the occipital horn of left ventricle and absence of the corpus callosum in one person [Escobar et al 2009]
- Epilepsy was reported in 13 individuals with Muenke syndrome by Agochukwu et al [2012]. More recently, 20 of 99 (20.2%) individuals with Muenke syndrome had a history of seizures [Kruszka et al 2016].
- One individual had a cranial nerve VI deficit leading to paralytic strabismus [Lowry et al 2001].

Ocular anomalies

- Strabismus is the most common ocular finding in Muenke syndrome. Children with Muenke syndrome also have a higher incidence of anisometropia, downward lateral canthal dystopia, and amblyopia [Jadico et al 2006].
- Ptosis of the upper eyelids has been described in 13 affected individuals [de Jong et al 2011, Kruszka et al 2016].
- Nystagmus has been described in four affected individuals [Jadico et al 2006, Singh et al 2014, Kruszka et al 2016].

Limb findings. Most individuals with Muenke syndrome have normal-appearing hands and feet with normal range of motion of all joints; many of the limb findings in Muenke syndrome are identified on radiographs, including short, broad middle phalanges of the fingers, absent or hypoplastic middle phalanges of the toes, carpal and/or tarsal fusion, and cone-shaped epiphyses [Hughes et al 2001, Kruszka et al 2016]. Broad thumbs and great toes have also been described in individuals with Muenke syndrome. Cutaneous syndactyly has been described in 13 affected individuals [Golla et al 1997, Passos-Bueno et al 1999, Chun et al 2002, Trusen et al 2003, Shah et al 2006, Baynam & Goldblatt 2010, de Jong et al 2011].

Obstructive sleep apnea, a common finding in craniosynostosis syndromes in general, is less prevalent in those with Muenke syndrome [Bannink et al 2011, Dentino et al 2015].

Penetrance

Penetrance is reduced. Some individuals heterozygous for the *FGFR3* p.Pro250Arg pathogenic variant have no clinical or radiographic features of Muenke syndrome [Robin et al 1998, Moko & Blandin de Chalain 2001, Kruszka et al 2016]. There was no sex-based difference in penetrance in a cohort of 106 individuals [Kruszka et al 2016].

Nomenclature

The phrase "Muenke nonsyndromic coronal craniosynostosis" is occasionally used to mean Muenke syndrome. The authors discourage the use of this phrase because it inaccurately implies a "non-genetic" cause of Muenke syndrome.

The term "Adelaide-type craniosynostosis" is no longer used to describe Muenke syndrome.

Prevalence

The birth prevalence of Muenke syndrome is approximately one in 30,000.

In a prospective study of 214 individuals with craniosynostosis born between 1993 and 2005, Morriss-Kay & Wilkie [2005] reported that of the 60 who had a specific molecular diagnosis, 28.5% had the p.Pro250Arg pathogenic variant; thus, 8% of the 214 individuals had Muenke syndrome.

Muenke syndrome is estimated to account for 25%-30% of all genetic causes of craniosynostosis [Morriss-Kay & Wilkie 2005, Wilkie et al 2010].

FGFR3 pathogenic variant p.Pro250Arg is estimated to occur at a rate of 7.6-8 x 10^{-6} per haploid genome, one of the highest known rates for a human transversion [Moloney et al 1997, Rannan-Eliya et al 2004].

Genetically Related (Allelic) Disorders

Other craniosynostosis phenotypes associated with germline pathogenic variants in *FGFR3* are summarized in Table 3a; allelic disorders not known to be associated with craniosynostosis are summarized in Table 3b.

Table 3a. Allelic Craniosynostosis Disorders

Disorder	*FGFR3* Pathogenic Variants [1]
Isolated unilateral coronal synostosis	c.749C>T (p.Pro250Leu) reported in 1 family [2]
Crouzon syndrome w/acanthosis nigricans	c.1172C>A (p.Ala391Glu) [3]

Table 3a. continued from previous page.

Disorder	*FGFR3* Pathogenic Variants [1]
Pfeiffer syndrome	c.1172C>A (p.Ala391Glu) reported in 1 person w/Pfeiffer syndrome [4]

1. Reference sequences: NM_000142.5; NP_000133.1
2. Schindler et al [2002]
3. Mulliken et al [1999]
4. Rymer et al [2019]

Table 3b. Other Clinically Distinct Allelic Disorders and Associated *FGFR3* Pathogenic Variants

Phenotype	MOI	*FGFR3* Pathogenic Variants [1]
Achondroplasia	AD	c.1138G>A (p.Gly380Arg) & c.1138G>C (p.Gly380Arg)
Camptodactyly, tall stature, & hearing loss (CATSHL) syndrome (OMIM 610474)	AD AR	c.1862G>A (p.Arg621His)
Hypochondroplasia	AD	Common pathogenic variants are c.1620C>A (p.Asn540Lys) & c.1620C>G (p.Asn540Lys)
Lacrimoauriculodentodigital syndrome (OMIM 149730)	AD	c.1537G>A (p.Asp513Asn)
Thanatophoric dysplasia (TD)	AD	c.1948A>G (p.Lys650Glu) is identified in >99% of persons w/TD type II
Severe achondroplasia w/developmental delay & acanthosis nigricans (SADDAN) syndrome (OMIM 616482)	AD	c.1949A>T (p.Lys650Met)

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Reference sequences: NM_000142.5; NP_000133.1

Differential Diagnosis

Syndromic craniosynostosis. Table 4 compares and contrasts Muenke syndrome with similar autosomal dominant craniosynostosis syndromes. Because of phenotypic overlap and/or mild phenotypes, clinical differentiation of these syndromes may be difficult.

Table 4. Comparison of Muenke Syndrome with Other *FGFR*-Related Craniosynostosis Syndromes and Saethre-Chotzen Syndrome

Gene	Syndrome	Features of Syndrome	
		Overlapping w/Muenke Syndrome	Distinguishing from Muenke Syndrome
FGFR1 *FGFR2* *FGFR3*	Pfeiffer syndrome [1]	• Bilateral coronal synostosis • Midface retrusion • Widely spaced eyes • Downslanted palpebral fissures • Strabismus • Highly arched palate • Brachydactyly • Normal intellect • Broad thumbs & great toes • Variable brachydactyly • Ocular proptosis	• Medial deviation of thumbs & great toes • Lateral deviation of thumbs & great toes away from other digits • Malformed & fused phalanges • Symphalangism • Mandibular prognathism
FGFR2	Apert syndrome	• Bilateral coronal synostosis • Broad thumbs & great toes • Widely spaced eyes • Downslanted palpebral fissures • Strabismus	• Disproportionately severe midface retrusion • Severe, symmetric soft tissue / bony syndactyly of fingers & toes • Lateral deviation of thumbs & great toes

Table 4. continued from previous page.

Gene	Syndrome	Features of Syndrome	
		Overlapping w/Muenke Syndrome	Distinguishing from Muenke Syndrome
		• Highly arched palate • Hearing loss • Ocular proptosis	• Acneiform eruptions
	Beare-Stevenson cutis gyrate [1]	• Bilateral coronal synostosis • Normal extremities	• Furrowed palms & soles • Widespread cutis gyrata & acanthosis nigricans • Prominent umbilicus • Moderate intellectual disability
	Crouzon syndrome [1]	• Bilateral coronal synostosis • Normal extremities • Normal intellect • Strabismus • Widely spaced eyes • Hearing deficit (conductive vs sensorineural in Muenke syndrome)	• Significant proptosis • Mandibular prognathism • Convex nasal ridge • Malar flattening • Progressive hydrocephalus
	Jackson-Weiss syndrome [1, 2]	• Bilateral coronal synostosis • Midface retrusion • Tarsal fusions • Broad great toes	• Metatarsal fusions • Abnormal tarsal bones • Medial deviation of great toes
TWIST1	Saethre-Chotzen syndrome	• Uni- or bilateral coronal synostosis • Brachycephaly • Facial asymmetry • Midface retrusion • Normal intellect or mild-to-moderate developmental delay • Ptosis • Widely spaced eyes • Strabismus • Downslanted palpebral fissures • High-arched palate • Brachydactyly	• Small ear pinna w/prominent crus • Syndactyly of fingers 2-3 • Low anterior hairline • Duplication of the distal phalanx of the hallux

1. See *FGFR* Craniosynostosis Syndromes Overview.
2. Jackson-Weiss syndrome is most likely limited to members of the original pedigree.

For an overview of other primary and secondary forms of craniosynostosis, see *FGFR* Craniosynostosis Syndromes Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Muenke syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Muenke Syndrome

System/Concern	Evaluation	Comment
Craniofacial	• Assessment of suture involvement by skull radiographs or preferably 3D skull CT • Assessment for hydrocephalus w/brain CT or MRI	
Hearing	Audiology assessment	
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl ADHD
Neurologic	Neurologic eval	Consider EEG if seizures are a concern.
Eyes	Assessment for exposure keratopathy	
	Ophthalmologic assessment	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, & strabismus
	Fundoscopy to assess for papilledema	Papilledema is present when intracranial pressure is ↑.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of Muenke syndrome to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Children with Muenke syndrome and craniosynostosis should be referred to a craniofacial clinic with pediatric experience. These individuals benefit most from a multidisciplinary approach to care. A craniofacial clinic associated with a major pediatric medical center usually includes a surgical team (craniofacial surgeon and neurosurgeon), clinical geneticist, ophthalmologist, otolaryngologist, pediatrician, radiologist, psychologist, dentist, audiologist, speech therapist, and social worker. Other disciplines are involved as needed.

Craniosynostosis. Depending on the severity, the first craniosynostosis repair is typically performed between ages three and six months. This procedure is usually transcranial (i.e., the skull is opened down to the dura so that the bones can be physically repositioned during a procedure such as a midface advancement). Early surgical reconstruction for craniosynostosis may reduce the risk for complications including cosmetic defects and sequelae related to increased intracranial pressure (e.g., behavioral changes, hydrocephalus due to venous outflow obstruction).

Newer approaches being performed include endoscopic strip craniectomy and posterior distraction.

- Endoscopic strip craniectomy is typically performed before the affected child reaches age three months. This minimally invasive surgery limits blood loss and has an overall long-term improved symmetry compared to traditional cranial vault remodeling and fronto-orbital advancement.
- Posterior distraction (PD) is used to manage individuals with severe brachycephaly or turribrachycephaly. It is a well-planned surgery using distractor devices. PD requires nuanced technical skill and the commitment of both the surgeon and the family several weeks postoperatively. PD has associated risks, yet severe complications are rare [Wiberg et al 2012, Thomas et al 2014, Salokorpi et al 2021].

Following craniosynostosis repair, the need for a second procedure is increased in those with Muenke syndrome compared to those with craniosynostosis without the defining pathogenic variant. The reasons for a second procedure vary by individual and can include the following:

- Severe initial clinical presentation requiring a staged repair
- Cranial vault abnormalities including temporal bulging and recurrent supraorbital retrusion requiring extracranial contouring (i.e., use of a cement such as calcium phosphate to contour the surface of the skull)
- Postoperative increased intracranial pressure (ICP)
- Recurrent deformity requiring a second transcranial repair:
    - The need for a surgical revision for aesthetic reasons (typically temporal bulging) has been reported in multiple series [Renier et al 2000, Cassileth et al 2001, Arnaud et al 2002, Thomas et al 2005, Honnebier et al 2008].
    - According to Thomas et al [2005], individuals with craniosynostosis and Muenke syndrome were more likely to require early intervention with a posterior release operation (at approximately age six months) to prevent excess frontal bulging than were those with other causes of craniosynostosis.
    - Seven of 29 individuals (24.1%) with the p.Pro250Arg pathogenic variant underwent a second surgery (6/7 had increased ICP) as compared to two (4.3%) of 47 without the pathogenic variant. This difference in reoperation rate was statistically significant (p=0.048) [Thomas et al 2005].
    - In the report of Honnebier et al [2008], 16 individuals with Muenke syndrome required a second procedure: seven required a second transcranial procedure, and 15 were expected to undergo extracranial contouring. Note that none had increased ICP.
    - However, a study by Ridgway et al [2011] challenges the above findings, reporting a frequency of frontal revision in individuals with Muenke syndrome who had fronto-orbital advancements that was lower than previously reported. This study found that the need for secondary revision procedures was inversely related to the age of the affected individual at the time of the initial repair. The location of the fused/synostotic suture, type of fixation, and the use of bone grafting did not have a significant effect on the need for revision.

In Muenke syndrome a discrepancy between severity of the craniofacial findings (e.g., severe midface retrusion, widely spaced eyes) and neurologic findings (e.g., increased ICP, hydrocephalus, structural brain anomalies, severe developmental delay, or severe intellectual disability) has been noted [Lajeunie et al 1999, Arnaud et al 2002, Honnebier et al 2008]: severe early clinical findings such as recurrent deformity and the need for a second major procedure did not correlate with postoperative risk for increased ICP.

Hearing loss. Hearing loss is often sensorineural. Standard treatments for hearing loss apply, including special accommodations for school-aged children, hearing aids, and (potentially) cochlear implants (see Hereditary Hearing Loss and Deafness Overview) [Agochukwu et al 2014b].

Developmental and neurobehavioral issues. Individuals with Muenke syndrome are at increased risk for developmental delay, intellectual disability, and behavioral issues [Maliepaard et al 2014, Yarnell et al 2015]; thus, referral for speech therapy and early intervention is indicated. Referral to a developmental and/or behavioral specialist for assessment and treatment is recommended.

Ocular abnormalities

- Strabismus surgery/correction is indicated to prevent amblyopia.
- Because surgical correction of craniosynostosis is a priority, delay in strabismus surgery in the first two years of life is common; however, earlier correction of strabismus should be considered to achieve binocularity.
- In those with proptosis, lubrication for exposure keratopathy is indicated.

Surveillance

Protocol-driven approaches to surveillance currently in use include those of Flapper et al [2009] and de Jong et al [2010]. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6).

Table 6. Recommended Surveillance for Individuals with Muenke Syndrome

System/Concern	Evaluation	Frequency
Hearing	Audiology eval	Annually or as indicated
Development	Monitor developmental progress & educational needs.	At each visit
Psychiatric/ Behavioral	Behavioral assessment	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Eyes	Ophthalmology assessment for strabismus	Annually or as indicated
Family/ Community	Assess family need for social work support, care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify as early as possible those who would benefit from institution of treatment and preventive measures (particularly in individuals affected with craniosynostosis, hearing loss, developmental delay, and/or cognitive disability). Evaluation includes targeted molecular genetic testing for the *FGFR3* c.749C>G (p.Pro250Arg) pathogenic variant.

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

Therapies Under Investigation

Mansour et al [2009] determined that in the mouse model of Muenke syndrome all mice had low-frequency sensorineural hearing loss. The characteristic sensorineural hearing loss is probably due to abnormal development of the auditory sensory epithelium of the inner ear, including excess pillar cells, too few Deiters cells, and extra outer hair cells in the organ of Corti. A further study revealed that the rescue of cochlear function and hearing loss phenotype of these mice is possible with a reduction in FGF-10, which normally activates FGFR-2b or FGFR-1b [Mansour et al 2013]. Aberrant signaling through the FGF signaling pathway that includes *FGFR3* may be the cause of the abnormal development of auditory sensory cells in Muenke syndrome [Agochukwu et al 2014a].

Animal models indicate that *FGFR3* is expressed at its highest levels in the developing central nervous system.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Muenke syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- More than half of individuals diagnosed with Muenke syndrome inherited the *FGFR3* p.Pro250Arg pathogenic variant from a parent [Kruszka et al 2016].
- A proband with Muenke syndrome may have the disorder as the result of a *de novo* pathogenic variant. *De novo* pathogenic variants causing Muenke syndrome appear to be exclusively of paternal origin [Rannan-Eliya et al 2004] and to be associated with advanced paternal age [Kruszka et al 2016].
- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for the parents of the proband include:
  - Physical examination and radiographs of the skull, hands, and feet;
  - Molecular genetic testing for the *FGFR3* p.Pro250Arg pathogenic variant to confirm the genetic status of the parents and to allow reliable recurrence risk counseling.

  Evaluation of the parents may determine that one is heterozygous for the p.Pro250Arg pathogenic variant but has a mild phenotype.
- If the p.Pro250Arg pathogenic variant is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with Muenke syndrome may appear to be negative because of subtle or absent clinical findings in a heterozygous parent or failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the p.Pro250Arg pathogenic variant.

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

- If a parent of the proband is affected and/or is known to have the defining *FGFR3* p.Pro250Arg pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. Because penetrance is reduced and the phenotype is variable within families, the manifestations in a sib who inherits the pathogenic variant cannot be predicted based on the phenotypes of other heterozygous family members (see Penetrance). Sibs who inherit the *FGFR3* p.Pro250Arg pathogenic variant may be more or less severely affected than

their parent(s). Uni- and bilateral coronal synostosis as well as absence of synostosis may be seen in individuals in the same family.

- If the *FGFR3* p.Pro250Arg pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *FGFR3* p.Pro250Arg but are clinically unaffected, sibs are still presumed to be at increased risk for Muenke syndrome because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

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

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *FGFR3* p.Pro250Arg pathogenic variant, the parent's family members are at risk.

Related Genetic Counseling Issues

Consideration of molecular genetic testing of young, at-risk family members is appropriate for guiding medical management (see Management, Evaluation of Relatives at Risk). Prior to testing sibs, parents, and extended family members, discussion should be held with a genetic counselor regarding the risks, benefits, and limitations of testing.

Generally, in individuals of school age and older who have no developmental issues, developmental delay, hearing loss, craniosynostosis, or other features of Muenke syndrome, the likelihood of Muenke syndrome is quite low, though the *FGFR3* p.Pro250Arg pathogenic variant has been identified in seemingly unaffected individuals [Kruszka et al 2016]. Children who inherit the *FGFR3* p.Pro250Arg pathogenic variant may be more or less severely affected than their parent(s). Uni- and bilateral coronal synostosis as well as absence of synostosis may be seen in individuals in the same family.

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *FGFR3* p.Pro250Arg pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for Muenke syndrome are possible.

Ultrasound examination. Craniosynostosis should be suspected when the cephalic index, cranial shape, or fetal face shape is abnormal [Tonni et al 2011]. Although difficult, prenatal diagnosis may be possible by ultrasound examination of the calvarial sutures. When present, additional craniofacial features of Muenke syndrome (i.e., midface hypoplasia, ocular hypertelorism) may also be apparent [Shaw et al 2011].

In a family known to have the pathogenic variant, if craniosynostosis or other craniofacial features (i.e., midface hypoplasia, ocular hypertelorism) are seen on prenatal ultrasound examination, the index of suspicion for Muenke syndrome should be high.

On prenatal ultrasound examination of twins with Muenke syndrome, Escobar et al [2009] found normal anatomy in one twin and congenital anomalies in the other twin; the diagnosis of Muenke syndrome was molecularly confirmed after birth in both twins.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

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

- **Born a Hero**
  www.bornahero.org
- **MedlinePlus**
  Muenke syndrome
- **Children's Craniofacial Association**
  Phone: 800-535-3643
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **Face Equality International**
  United Kingdom
  faceequalityinternational.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424
  Craniosynostosis

Molecular Genetics

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

Table A. Muenke Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FGFR3	4p16.3	Fibroblast growth factor receptor 3	FGFR3 @ LOVD	FGFR3	FGFR3

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

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

134934	FIBROBLAST GROWTH FACTOR RECEPTOR 3; FGFR3
602849	MUENKE SYNDROME; MNKES

Molecular Pathogenesis

The fibroblast growth factor receptor (FGFR) family is a group of receptor tyrosine kinases. FGFRs 1-4 have an extracellular ligand-binding domain containing three immunoglobulin-like loops, a single-pass transmembrane

domain, and a split intracellular kinase domain. FGFRs bind fibroblast growth factors (FGFs) and dimerize to affect downstream intracellular signaling [Green et al 1996]. FGFR3 negatively regulates chondrocyte differentiation and proliferation in developing endochondral bone (appendicular skeleton) [Ornitz & Marie 2002].

The genetics of intramembranous bone (skull vault) formation are complex, and the role of FGFR3 is not yet well understood. FGFR3 is detected in coronal suture osteogenic fronts but at lower levels than FGFR1 and FGFR2 [Iseki et al 1999]. FGFR3 is mainly expressed in mature chondrocytes of the cartilage growth plate [Cunningham et al 2007]. FGFR3 mRNA is found in its highest amounts in the developing central nervous system [Robin 1999]. It is also present in the skeletal precursors for all bones during the period of endochondral ossification and resting cartilage [Robin 1999].

The p.Pro250Arg pathogenic variant results in enhanced FGF binding [Ibrahimi et al 2004]. This pathogenic variant is located in the linker region between the second and third immunoglobulin-like domains (see Figure 1) [Park et al 1995, Wilkie et al 1995]. Kinetic ligand binding studies and x-ray crystallography of linker region pathogenic variants demonstrate that the pathogenic variant results in increased ligand affinity (FGF9) and altered specificity [Cunningham et al 2007]. Overactivation of FGFR3 appears to lead to craniosynostosis because bone differentiation is accelerated [Funato et al 2001].

Mechanism of disease causation. Gain of function

Table 7. Notable *FGFR3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_000142.5 NP_000133.1	c.749C>G	p.Pro250Arg	Pathogenic variant assoc w/ Muenke syndrome
	c.749C>T	p.Pro250Leu	See Genetically Related Disorders.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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Figure 1. Schema of the FGFR3 protein

The loops represent the three immunoglobulin domains (left to right: IgI, IgII, IgIII). The p.Pro250Arg protein change (indicated with a black dot) is in the linker region between the second and third immunoglobulin domains. The grey boxes following the third immunoglobulin domain are (left to right): transmembrane domain (small grey box); first and second tyrosine kinase domains (2nd and 3rd dark grey boxes, respectively) [Cunningham et al 2007].

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- 30 March 2023 (sw) Comprehensive update posted live
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- 10 May 2006 (me) Review posted live
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References

Literature Cited

Agochukwu NB, Solomon BD, Benson LJ, Muenke M. Talocalcaneal coalition in Muenke syndrome: report of a patient, review of the literature in FGFR-related craniosynostoses, and consideration of mechanism. Am J Med Genet A. 2013;161A:453–60. PubMed PMID: 23378035.

Agochukwu NB, Solomon BD, Muenke M. Hearing loss in syndromic craniosynostoses: introduction and consideration of mechanisms. Am J Audiol. 2014a;23:135–41. PubMed PMID: 24686979.

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

Agochukwu NB, Solomon BD, Muenke M. Impact of genetics on the diagnosis and clinical management of syndromic craniosynostoses. Childs Nerv Syst. 2012;28:1447–63. PubMed PMID: 22872262.

Arnaud E, Meneses P, Lajeunie E, Thorne JA, Marchac D, Renier D. Postoperative mental and morphological outcome for nonsyndromic brachycephaly. Plast Reconstr Surg. 2002;110:6–12. PubMed PMID: 12087222.

Bannink N, Maliepaard M, Raat H, Joosten KF, Mathijssen IM. Obstructive sleep apnea-specific quality of life and behavioral problems in children with syndromic craniosynostosis. J Dev Behav Pediatr. 2011;32:233–8. PubMed PMID: 21297497.

Baynam GS, Goldblatt J. A child with an FGFR3 mutation, a laterality disorder and an hepatoblastoma: novel associations and possible gene-environment interactions. Twin Res Hum Genet. 2010;13:297–300. PubMed PMID: 20707699.

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 PMID: 8841188.

Cassileth LB, Bartlett SP, Glat PM, Gripp KW, Muenke M, Zackai EH, Whitaker LA. Clinical characteristics of patients with unicoronal synostosis and mutations of fibroblast growth factor receptor 3: a preliminary report. Plast Reconstr Surg. 2001;108:1849–54. PubMed PMID: 11743367.

Chun K, Teebi AS, Jung JH, Kennedy S, Laframboise R, Meschino WS, Nakabayashi K, Scherer SW, Ray PN, Teshima I. Genetic analysis of patients with the Saethre-Chotzen phenotype. Am J Med Genet. 2002;110:136–43. PubMed PMID: 12116251.

Cunningham ML, Seto ML, Ratisoontorn C, Heike CL, Hing AV. Syndromic craniosynostosis: from history to hydrogen bonds. Orthod Craniofac Res. 2007;10:67–81. PubMed PMID: 17552943.

de Jong T, Bannink N, Bredero-Boelhouwer HH, van Veelen ML, Bartels MC, Hoeve LJ, Hoogeboom AJ, Wolvius EB, Lequin MH, van der Meulen JJ, van Adrichem LN, Vaandrager JM, Ongkosuwito EM, Joosten KF, Mathijssen IM. Long-term functional outcome in 167 patients with syndromic craniosynostosis; defining a syndrome-specific risk profile. J Plast Reconstr Aesthet Surg. 2010;63:1635–41. PubMed PMID: 19913472.

de Jong T, Mathijssen IM, Hoogeboom AJ. Additional phenotypic features of Muenke syndrome in 2 Dutch families. J Craniofac Surg. 2011;22:571–5. PubMed PMID: 21403557.

Dentino K, Ganjawalla K, Inverso G, Mulliken JB, Padwa BL. Upper Airway Length is Predictive of Obstructive Sleep Apnea in Syndromic Craniosynostosis. J Oral Maxillofac Surg. 2015;73:S20–5. PubMed PMID: 26608151.

Didolkar MM, Vinson EN, Gaca AM. A young patient with polyarthralgia and hearing loss: a case report of Muenke syndrome. Skeletal Radiol. 2009;38:1011–4. PubMed PMID: 19449001.

Doumit GD, Sidaoui J, Meisler E, Papay FA. Squamosal suture craniosynostosis in Muenke syndrome. J Craniofac Surg. 2014;25:429–31. PubMed PMID: 24448525.

Escobar LF, Hiett AK, Marnocha A. Significant phenotypic variability of Muenke syndrome in identical twins. Am J Med Genet A. 2009;149A:1273–6. PubMed PMID: 19449410.

Flapper WJ, Anderson PJ, Roberts RM, David DJ. Intellectual outcomes following protocol management in Crouzon, Pfeiffer, and Muenke syndromes. J Craniofac Surg. 2009;20:1252–5. PubMed PMID: 19625842.

Funato N, Ohtani K, Ohyama K, Kuroda T, Nakamura M. Common regulation of growth arrest and differentiation of osteoblasts by helix-loop-helix factors. Mol Cell Biol. 2001;21:7416–28. PubMed PMID: 11585922.

Golla A, Lichmer P, von Gernet S, Winterpacht A, Fairley J, Murken J, Schuffenhauer S. Phenotypic expression of the fibroblast growth factor receptor 3 (FGFR3) mutation P250R in a large craniosynostosis family. J Med Genet. 1997;34:683–4. PubMed PMID: 9279764.

Green PJ, Walsh FS, Doherty P. Promiscuity of fibroblast growth factor receptors. Bioessays. 1996;18:639–46. PubMed PMID: 8760337.

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;120A:88–91. PubMed PMID: 12794698.

Hollway GE, Suthers GK, Battese KM, Turner AM, David DJ, Mulley JC. Deafness due to Pro250Arg mutation of FGFR3. Lancet. 1998;351:877–8. PubMed PMID: 9525367.

Honnebier MB, Cabiling DS, Hetlinger M, McDonald-McGinn DM, Zackai EH, Bartlett SP. The natural history of patients treated for FGFR3-associated (Muenke-type) craniosynostosis. Plast Reconstr Surg. 2008;121:919–31. PubMed PMID: 18317141.

Hughes J, Nevin NC, Morrison PJ. Familial craniosynostosis due to Pro250Arg mutation in the fibroblast growth factor receptor 3 gene. Ulster Med J. 2001;70:47–50. PubMed PMID: 11428324.

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 PMID: 14613973.

Iseki S, Wilkie AO, Morriss-Kay GM. Fgfr1 and Fgfr2 have distinct differentia. Development. 1999;126:5611–20. PubMed PMID: 10572038.

Jadico SK, Huebner A, McDonald-McGinn DM, Zackai EH, Young TL. Ocular phenotype correlations in patients with TWIST versus FGFR3 genetic mutations. J AAPOS. 2006;10:435–44. PubMed PMID: 17070479.

Keller MK, Hermann NV, Darvann TA, Larsen P, Hove HD, Christensen L, Schwartz M, Marsh JL, Kreiborg S. Craniofacial morphology in Muenke syndrome. J Craniofac Surg. 2007;18:374–86. PubMed PMID: 17414289.

Kruszka P, Addissie YA, Yarnell CM, Hadley DW, Guillen Sacoto MJ, Platte P, Paelecke Y, Collmann H, Snow N, Schweitzer T, Boyadjiev SA, Aravidis C, Hall SE, Mulliken JB, Roscioli T, Muenke M. Muenke syndrome: An international multicenter natural history study. Am J Med Genet A. 2016;170A:918–29. PubMed PMID: 26740388.

Lajeunie E, El Ghouzzi V, Le Merrer M, Munnich A, Bonaventure J, Renier D. Sex related expressivity of the phenotype in coronal craniosynostosis caused by the recurrent P250R FGFR3 mutation. J Med Genet. 1999;36:9–13. PubMed PMID: 9950359.

Lowry RB, Jabs EW, Graham GE, Gerritsen J, Fleming J. Syndrome of coronal craniosynostosis, Klippel-Feil anomaly, and Sprengel shoulder with and without Pro250Arg mutation in the FGFR3 gene. Am J Med Genet. 2001;104:112–9. PubMed PMID: 11746040.

Maliepaard M, Mathijssen IM, Oosterlaan J, Okkerse JM. Intellectual, behavioral, and emotional functioning in children with syndromic craniosynostosis. Pediatrics. 2014;133:e1608–15. PubMed PMID: 24864183.

Mansour SL, Li C, Urness LD. Genetic rescue of Muenke syndrome model hearing loss reveals prolonged FGF-dependent plasticity in cochlear supporting cell fates. Genes Dev. 2013;27:2320–31. PubMed PMID: 24145799.

Mansour SL, Twigg SRF, Freeland RM, Wall SA, Li C, Wilkie AOM. Hearing loss in a mouse model of Muenke syndrome. Hum Mol Genet. 2009;18:43–50. PubMed PMID: 18818193.

Moko SB, Blandin de Chalain TM. New Zealand Maori family with the pro250arg fibroblast growth factor receptor 3 mutation associated with craniosynostosis. J Craniomaxillofac Surg. 2001;29:22–4. PubMed PMID: 11467490.

Moloney DM, Wall SA, Ashworth GJ, Oldridge M, Glass IA, Francomano CA, Muenke M, Wilkie AO. Prevalence of Pro250Arg mutation of fibroblast growth factor receptor 3 in coronal craniosynostosis. Lancet. 1997;349:1059–62. PubMed PMID: 9107244.

Morriss-Kay GM, Wilkie AOM. Growth of the normal skull vault and its alteration in craniosynostosis: Insights from human genetics and experimental studies. J Anat. 2005;207:637–53. PubMed PMID: 16313397.

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, Zackai EH. A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) defines a new craniosynostosis syndrome. Am J Hum Genet. 1997;60:555–64. PubMed PMID: 9042914.

Mulliken JB, Steinberger D, Kunze S, Muller U. Molecular diagnosis of bilateral coronal synostosis. Plast Reconstr Surg. 1999;104:1603–15. PubMed PMID: 10541159.

Ornitz DM, Marie PJ. FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. Genes Dev. 2002;16:1446–65. PubMed PMID: 12080084.

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

Passos-Bueno MR, Wilcox WR, Jabs EW, Sertié AL, Alonso LG, Kitoh H. Clinical spectrum of fibroblast growth factor receptor mutations. Hum Mutat. 1999;14:115–25. PubMed PMID: 10425034.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Rannan-Eliya SV, Taylor IB, De Heer IM, Van Den Ouweland AM, Wall SA, Wilkie AO. Paternal origin of FGFR3 mutations in Muenke-type craniosynostosis. Hum Genet. 2004;115:200–7. PubMed PMID: 15241680.

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 PMID: 10761652.

Ridgway EB, Wu JK, Sullivan SR, Vasudavan S, Padwa BL, Rogers GF, Mulliken JB. Craniofacial growth in patients with FGFR3 Pro250Arg mutation after fronto-orbital advancement in infancy. J Craniofac Surg. 2011;22:455–61. PubMed PMID: 21403567.

Robin NH. Molecular genetic advances in understanding craniosynostosis. Plast Reconstr Surg. 1999;103:1060–70. PubMed PMID: 10077104.

Robin NH, Scott JA, Cohen AR, Goldstein JA. Nonpenetrance in FGFR3-associated coronal synostosis syndrome. Am J Med Genet. 1998;80:296–7. PubMed PMID: 9843059.

Rymer K, Shiang R, Hsiung A, Pandya A, Bigdeli T, Webb BT, Rhodes J. Expanding the phenotype for the recurrent p.Ala391Glu variant in FGFR3: Beyond crouzon syndrome and acanthosis nigricans. Mol Genet Genomic Med. 2019;7:e656. PubMed PMID: 31016899.

Salokorpi N, Satanin L, Teterin I, Sinikumpu JJ, Serlo W. Posterior vault distraction technique: how I do it. Childs Nerv Syst. 2021;37:3127–36. PubMed PMID: 34032915.

Schindler S, Friedrich M, Wagener H, Lorenz B, Preising MN. Heterozygous P250L mutation of fibroblast growth factor receptor 3 in a case of isolated craniosynostosis. J Med Genet. 2002;39:764–6. PubMed PMID: 12362036.

Shah PS, Siriwardena K, Taylor G, Steele L, Ray P, Blaser S, Chitayat D. Sudden infant death in a patient with FGFR3 P250R mutation. Am J Med Genet A. 2006;140:2794–6. PubMed PMID: 17103449.

Shaw A, Petersen OB, Chitty LS. Prenatal diagnosis of craniosynostosis: sonographic features of Muenke syndrome. J Obstet Gynaecol. 2011;31:770–1. PubMed PMID: 22085076.

Singh A, Goyal M, Kumar S, Kress W, Kapoor S. Phenotypic variability in two families of Muenke syndrome with FGFR3 mutation. Indian J Pediatr. 2014;81:1230–2. PubMed PMID: 24705944.

Thomas GP, Wall SA, Jayamohan J, Magdum SA, Richards PG, Wiberg A, Johnson D. Lessons learned in posterior cranial vault distraction. J Craniofac Surg. 2014;25:1721–7. PubMed PMID: 25162545.

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 PMID: 15915095.

Tonni G, Panteghini M, Rossi A, Baldi M, Magnani C, Ferrari B, Lituania M. Craniosynostosis: prenatal diagnosis by means of ultrasound and SSSE-MRI. Family series with report of neurodevelopmental outcome and review of the literature. Arch Gynecol Obstet. 2011;283:909–16. PubMed PMID: 20811900.

Trusen A, Beissert M, Collmann H, Darge K. The pattern of skeletal anomalies in the cervical spine, hands and feet in patients with Saethre-Chotzen syndrome and Muenke-type mutation. Pediatr Radiol. 2003;33:168–72. PubMed PMID: 12612814.

van der Meulen J, van den Ouweland A, Hoogeboom J. Trigonocephaly in Muenke syndrome. Am J Med Genet A. 2006;140:2493–4. PubMed PMID: 17036334.

Wiberg A, Magdum S, Richards PG, Jayamohan J, Wall SA, Johnson D. Posterior calvarial distraction in craniosynostosis - an evolving technique. J Craniomaxillofac Surg. 2012;40:799–806. PubMed PMID: 22560871.

Wilkie AO, Byren JC, Hurst JA, Jayamohan J, Johnson D, Knight SJ, Lester T, Richards PG, Twigg SR, Wall SA. Prevalence and complications of single gene and chromosomal disorders in craniosynostosis. Pediatrics. 2010;126:e391–400. PubMed PMID: 20643727.

Wilkie AOM, Slaney SF, Oldridge M., Poole MD, Ashworth GJ, Hockley AD, Hayward RD, David DJ, Pulleyn LK, Rutland P, Malcolm S, Winter RM, Reardon W. Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. Nat Genet. 1995;9:165–72. PubMed PMID: 7719344.

Yarnell CM, Addissie YA, Hadley DW, Guillen Sacoto MJ, Agochukwu NB, Hart RA, Wiggs EA, Platte P, Paelecke Y, Collmann H, Schweitzer T, Kruszka P, Muenke M. Executive Function and Adaptive Behavior in Muenke Syndrome. J Pediatr. 2015;167:428–34. PubMed PMID: 26028288.

Yu JE, Park DH, Yoon SH. A Korean family with the Muenke syndrome. J Korean Med Sci. 2010;25:1086–9. PubMed PMID: 20592905.

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