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

NLM Citation: Kruszka P, Addissie YA, Agochukwu NB, et al. Muenke Syndrome. 2006 May 10 [Updated 2016 Nov 10]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Muenke Syndrome

Paul Kruszka, MD, MPH,[1] Yonit A Addissie, BA,[1] Nneamaka B Agochukwu, MD,[2] Emily S Doherty, MD, FAAP, FACMG,[3] and Maximilian Muenke, MD, FACMG[1]

Created: May 10, 2006; Updated: November 10, 2016.

Summary

Clinical characteristics

Muenke syndrome is defined by the presence of the specific *FGFR3* pathogenic variant – c.749C>G – that results in the protein change p.Pro250Arg. 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 (reduced anteroposterior dimension of the skull), 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); midface retrusion (usually mild); and highly arched palate or cleft lip and palate. Strabismus is common. Other findings can include: hearing loss (in 33%-100% of affected individuals); developmental delay (~33%); epilepsy; intracranial anomalies; intellectual disability; carpal bone and/or tarsal bone fusions; brachydactyly, broad toes, broad thumbs, and/or clinodactyly; and radiographic findings of thimble-like (short and broad) middle phalanges and/or cone-shaped epiphyses. Phenotypic variability is considerable even within the same family. 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).

Management

Treatment of manifestations: Children with Muenke syndrome and craniosynostosis are best managed by a pediatric craniofacial clinic that typically includes a craniofacial surgeon and neurosurgeon, clinical geneticist,

Author Affiliations: 1 National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland; Email: paul.kruszka@nih.gov; Email: yonit.addissie@nih.gov; Email: mamuenke@mail.nih.gov. 2 Clinical Research Training Program, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, University of Kentucky, Lexington, Kentucky; Email: nneamaka.agochukwu@nih.gov. 3 Carilion Pediatric Clinic, Roanoke, Virginia; Email: esdoherty@carilionclinic.org.

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 months.

Postoperative increased intracranial pressure and/or the need for secondary or tertiary extracranial contouring may occur. The need for secondary revision procedures is inversely related to the age of the affected individual at the time of initial repair. The location of the fused/synostotic suture, type of fixation, and the use of bone grafting do not have a significant effect on the need for revision.

Standard treatments for sensorineural hearing loss; early speech therapy and intervention programs for those with developmental delay, intellectual impairment, behavioral problems, and/or hearing loss; surgical correction for strabismus; lubrication for exposure keratopathy.

Prevention of secondary complications: Early surgical reconstruction for craniosynostosis may reduce the risk for complications including sequelae related to increased intracranial pressure (e.g., behavioral changes).

Surveillance: Affected individuals benefit from integrated multidisciplinary care and protocol-driven management from birth to maturity that includes: annual multidisciplinary reviews and periodic review by a social work team; regular developmental assessments; periodic repeat audiograms to screen for acquired or progressive hearing loss; periodic assessment for strabismus.

Genetic counseling

Muenke syndrome is inherited in an autosomal dominant manner with incomplete penetrance and variable expressivity. If the defining *FGFR3* pathogenic variant cannot be detected in either parent of a proband, germline mosaicism in a parent or a *de novo* pathogenic variant in the proband are possible. Each child of an individual with Muenke syndrome has a 50% chance of inheriting the pathogenic variant. Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant has been identified in the family. Prenatal ultrasound examination may be used as an adjunct to prenatal genetic testing.

Diagnosis

Although the diagnosis of Muenke syndrome is suggested by clinical findings, it is established by the presence of the *FGFR3* pathogenic variant c.749C>G (p.Pro250Arg). The phenotype is quite variable and ranges from no detectable clinical manifestations to the presence of craniosynostosis along with other classic features.

Suggestive Findings

Muenke syndrome **should be suspected** in individuals with the following clinical and radiographic findings.

Clinical features

- Facial asymmetry
- Brachycephaly (reduced anteroposterior dimension of the skull), turribrachycephaly (a "tower-shaped" skull), or cloverleaf skull
- Sutural ridging over both (or less commonly one) of the coronal sutures accompanied by:
  - Ipsilateral
    - Flattening of the forehead
    - Elevation of the superior orbital rim
    - Elevation of the eyebrow
    - Anterior placement of the ear

        - Deviation of the nasal root
    - Contralateral
        - 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, Graham et al 1998, Kruszka et al 2016]
    - Epiphyseal coning [Muenke et al 1997, Graham et al 1998, Kruszka et al 2016]

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 performed first. Note: Targeted analysis for the c.749C>G pathogenic variant in *FGFR3* is rarely performed because the clinical features of Muenke syndrome overlap with those of other craniosynostosis conditions 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 at the most reasonable cost 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]	>99% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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

Craniosynostosis and craniofacial features. Coronal synostosis may be bilateral (~2/3 of affected individuals) or unilateral (~1/3 of affected individuals) [Renier et al 2000, 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) [Golla et al 1997, van der Meulen et al 2006, Doumit et al 2014, Kruszka et al 2016].

Craniosynostosis is not always present in individuals with Muenke syndrome:

- In 72 individuals from 24 families, nine persons (12.5%) known to be heterozygous for the *FGFR3* p.Pro250Arg pathogenic variant had no evidence of craniosynostosis [Renier et al 2000].
- In a family of seven, five had coronal synostosis and two were phenotypically normal [Moko & Blandin de Chalain 2001]. All seven individuals were heterozygous for the *FGFR3* p.Pro250Arg pathogenic variant.
- In a large international cohort of individuals with Muenke syndrome, 16 (15.5%) of 103 did not have craniosynostosis [Kruszka et al 2016].

In these cases, extracranial findings (i.e., hearing loss [often mild to moderate], radiographic findings of carpal and tarsal fusions, short and broad middle phalanges, and cone-shaped epiphysis), when present, helped support the diagnosis of Muenke syndrome.

Craniofacial features that may result from craniosynostosis are summarized in Suggestive Findings. Rarer craniofacial features include ptosis, malar flattening, a short nose with anteverted nares, an overhanging nasal tip, deviation of the nasal septum, a short nose with a depressed nasal bridge, high-arched palate and cleft lip and/or palate, dental malocclusion, mild retrognathia, hypoplastic auricles, and low-set ears.

Hearing loss. Initial studies revealed that at least one third of individuals with Muenke syndrome have mild to moderate sensorineural hearing loss [Muenke et al 1997, Kress et al 2006, de Jong et al 2010], with some even suggesting that all individuals with Muenke syndrome are likely to have some degree of hearing loss, usually mild [Doherty et al 2007, Honnebier et al 2008, Mansour et al 2009, de Jong et al 2011b]. 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].

- In a large-cohort international study, more than 70% of individuals with Muenke syndrome had hearing loss, with a majority (70.8%) having bilateral sensorineural hearing loss and the remainder having conductive (22%) and mixed forms (8.6%).

- Overall, a majority of hearing loss observed in craniosynostosis syndromes is conductive, except in Muenke syndrome, where sensorineural hearing loss is more likely [de Jong et al 2010, Agochukwu et al 2014b].
- Some children with Muenke syndrome and craniosynostosis develop hearing loss despite passing their newborn hearing screens [Doherty & Muenke, personal observation]. Additionally, some affected individuals may have hearing loss that progresses or becomes more severe as they age.
- Some individuals with Muenke syndrome 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 affected individuals.

Developmental delay and behavioral functioning. Developmental delay and/or intellectual disability, usually mild, has been reported in approximately one third of individuals [Muenke et al 1997, Kress et al 2006]. Compared to normative populations, individuals with Muenke syndrome have also been reported to be at increased risk for developing some behavioral and emotional problems [Maliepaard et al 2014, Yarnell et al 2015].

In a large international study of Muenke syndrome, 40.8% were reported to have intellectual disability and 66.3% had developmental delay, with speech delay the most common type (61.1%) [Kruszka et al 2016]. Approximately 24% had a diagnosis of ADHD.

- In a study of intellectual outcomes following protocol management in four persons with Muenke syndrome followed from birth to skeletal maturity compared to persons with Crouzon syndrome and Pfeiffer syndrome, Flapper et al [2009] found that individuals with Muenke syndrome and Pfeiffer syndrome were more likely to be intellectually impaired than were individuals with Crouzon syndrome. One of the four with Muenke syndrome had moderate intellectual disability (IQ <70) and a history of behavioral problems; two had borderline intellectual disability (IQ 70-80) and required special education; and one was of average intelligence (IQ 90-110), completed high school without difficulty, and is currently training to be a pilot.
- In a study by de Jong et al [2012] of individuals with syndromic craniosynostosis, it was found that all of the studied syndromes had a high prevalence of speech delay. In this study, cognitive delay was mainly reported in Apert, Crouzon, and Muenke syndromes. A study of syndromic craniosynostosis by Bannink et al [2011] found behavioral problems to be more common in boys with Apert and Muenke syndromes, with a prevalence of 67% and 50%, respectively.
- One study found a slightly lower IQ in individuals with craniosynostosis with Muenke syndrome compared to individuals with craniosynostosis who do not have the defining pathogenic variant [Arnaud et al 2002].
- After evaluating 13 children with Muenke syndrome, a study by Maliepaard et al [2014] found that children with Muenke syndrome had more social, attention, and inattention problems compared to a normative population and children with other craniosynostosis syndromes.
- In a cohort on 44 affected persons, Yarnell et al [2015] found that individuals with Muenke syndrome were at increased risk for developing adaptive and executive functioning problems compared to their unaffected (mutation negative) sibs and the normative population. 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 pathogenic *FGFR3* p.Pro250Arg 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], who was 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 (20.2%) of 99 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 [Yu et al 2010], with one large study reporting an incidence of 31/69 (45%) [Kruszka et al 2016] and another study finding strabismus in 14 (39%) of 26 individuals [de Jong et al 2010].

- Compared to the average pediatric population, children with Muenke syndrome have a higher incidence of strabismus (66%), anisometropia, epicanthal fold changes, widely spaced eyes, 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 2011a, 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; therefore, many of the limb findings in Muenke syndrome are identified during the diagnostic evaluation when radiographs reveal findings such as 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 toes and great thumbs 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 2011a].

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

Minor clinical signs / asymptomatic heterozygotes

- 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].
- Some individuals with Muenke syndrome have minor clinical signs such as macrocephaly [Gripp et al 1998] and subtle facial findings without craniosynostosis [Gripp et al 1998, Robin et al 1998, Moko & Blandin de Chalain 2001, Sabatino et al 2004, Didolkar et al 2009]; some appear clinically unaffected until their radiographs are examined [Muenke et al 1997]. These individuals may not come to medical attention until the birth of a more severely affected child.

Penetrance

Penetrance is reduced. In a familial study of seven affected individuals, six of eight individuals had coronal synostosis and two of eight were phenotypically normal [Moko & Blandin de Chalain 2001], yielding a penetrance of approximately 75% for that family.

There was no gender difference in penetrance and severity of craniosynostosis in a large international cohort of individuals with Muenke syndrome [Kruszka et al 2016]. In this study involving 106 people, 50% of females had bilateral coronal craniosynostosis compared to 44.4% of males (p=0.84), and the penetrance of craniosynostosis trait was similarly prevalent in males (86.7%) and females (82.8%). Previous smaller studies have found penetrance to be higher in females than in males [Moloney et al 1997, Lajeunie et al 1999, Doherty et al 2007, Honnebier et al 2008, Solomon & Muenke 2010].

Nomenclature

Several terms in the literature may be confusing to the reader:

- The term "nonsyndromic" means that a condition does not fit the pattern of a recognizable genetic syndrome [Mulliken 2002]. The term "nonsyndromic craniosynostosis" is variably used either:
  - As a synonym for single-suture craniosynostosis because most instances of single-suture craniosynostosis are of unknown etiology. However, the two terms are not identical in meaning.

    OR
  - To describe bilateral coronal suture synostosis that is not identifiable as a classic syndrome (e.g., Pfeiffer syndrome, Crouzon syndrome). When appropriate, the authors suggest the alternate terms "nonspecific craniosynostosis" or "unclassified brachycephaly."
- 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.
- An individual with "isolated craniosynostosis" has no extracranial manifestations [Cohen & MacLean 2000]. However, some authors use the term "isolated craniosynostosis" to mean that only one type of suture (e.g., coronal, sagittal) is fused. The correct term for uni- or bilateral premature fusion of one suture is "simple craniosynostosis." "Complex craniosynostosis" is correctly used to describe the involvement of two or more sutures.
- In the field of genetics, the term "sporadic" has been used to describe a variety of disparate phenomena. The term "sporadic craniosynostosis" is used by some authors to mean a case without a family history. However, "sporadic craniosynostosis" may incorrectly imply a low recurrence risk. The correct term for a single occurrence of Muenke syndrome in a family is "simplex."
- 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 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].

The c.749C>G pathogenic variant (p.Pro250Arg) in *FGFR3* is estimated to occur at a rate of $7.6\text{-}8\text{x}10^{-6}$ 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

Table 2. Clinically Distinct Disorders and their Causative *FGFR3* Pathogenic Variants

Disorder	*FGFR3* Pathogenic Variant(s) [1]	Reference
Thanatophoric dysplasia type 1	• p.Arg248Cys • p.Ser249Cys • p.Gly370Cys • p.Ser371Cys • p.Tyr373Cys • p.Lys650Glu • Several types of codon 807 substitutions	*GeneReview*
Achondroplasia	• p.Gly380Arg	*GeneReview*
Hypochondroplasia	• p.Asn540Lys (accounts for 60%-65% of affected persons) • Pathogenic variants dispersed in *FGFR3*	*GeneReview*
Lacrimoauriculodentodigital syndrome	• p.Asp513Asn	OMIM 149730
Camptodactyly, tall stature, and hearing loss (CATSHL) syndrome	• p.Arg621His	OMIM 610474
Crouzon syndrome with acanthosis nigricans (Crouzonodermoskeletal syndrome)	• p.Ala391Glu	*GeneReview*

1. Note: Amino acid changes are given as in the original publications.

Note: An individual with isolated unilateral coronal synostosis and her mildly affected mother were found to be heterozygous for a single-nucleotide variant in *FGFR3* resulting in p.Pro250Leu [Schindler et al 2002]. Although Schindler et al [2002] considered this family to have Muenke syndrome, it is not clear if these individuals (who have a different pathogenic variant at the same position as the defining p.Pro250Arg pathogenic variant) actually have Muenke syndrome because no additional individuals with a phenotype resembling Muenke syndrome have been reported to have missense variants at codon 250 encoding a substitution other than proline to arginine.

Differential Diagnosis

Unclassified brachycephaly refers to bilateral coronal synostosis in individuals who do not have any of the classic craniosynostosis syndromes (e.g., Pfeiffer syndrome, Crouzon syndrome). Following discovery of the *FGFR3* p.Pro250Arg pathogenic variant, one survey of a group with unclassified brachycephaly found that 52% had Muenke syndrome [Mulliken et al 1999].

Syndromic craniosynostosis. Table 3 compares and contrasts Muenke syndrome with similar craniosynostosis syndromes. Because of phenotypic overlap and/or mild phenotypes, clinical differentiation of these syndromes may be difficult.

Table 3. A Comparison of Muenke Syndrome with Other *FGFR*-Related Craniosynostosis Syndromes and Saethre-Chotzen Syndrome

Craniosynostosis Phenotype	"Classic" Features Common to Muenke Syndrome	Features Unlike Muenke Syndrome
Crouzon syndrome	• 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

Table 3. continued from previous page.

Craniosynostosis Phenotype	"Classic" Features Common to Muenke Syndrome	Features Unlike Muenke Syndrome
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
Pfeiffer syndrome type 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	• Medial deviation of thumbs & great toes • Lateral deviation of thumbs & great toes away from other digits • Malformed & fused phalanges • Symphalangism • Mandibular prognathism • Ocular proptosis
Jackson-Weiss syndrome [1]	• Bilateral coronal synostosis • Midface retrusion • Tarsal fusions • Broad great toes	• Metatarsal fusions • Abnormal tarsal bones • Medial deviation of great toes
Apert syndrome	• Bilateral coronal synostosis • Broad great toes • Widely spaced eyes • Downslanted palpebral fissures • Strabismus • Highly arched palate • Hearing loss	• Disproportionately severe midface retrusion • Ocular proptosis • Severe, symmetric soft tissue/bony syndactyly of fingers & toes • Broad thumbs • Lateral deviation of thumbs & great toes • Acneiform eruptions
Beare-Stevenson cutis gyrata	• Bilateral coronal synostosis • Normal extremities	• Furrowed palms & soles • Widespread cutis gyrata & acanthosis nigricans • Prominent umbilicus • Moderate intellectual disability

1. Jackson-Weiss syndrome is most likely limited to members of the original pedigree.

An identical proline-to-arginine variant occurs at analogous positions in *FGFR1*, *FGFR2*, and *FGFR3* (Figure 1):

- p.Pro252Arg in *FGFR1* causes Pfeiffer syndrome (*FGFR1* reference sequences NM_023110.2, NP_075598.2).
- p.Pro253Arg in *FGFR2* causes Apert syndrome (*FGFR2* reference sequences NM_022970.2, NP_075259.2).
- p.Pro250Arg in *FGFR3* causes Muenke syndrome (see Table 4).

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

Nonspecific craniosynostosis. Table 4 summarizes the detection rate for the p.Pro250Arg pathogenic variant among large craniosynostosis populations with nonspecific phenotypes.

Table 4. Craniosynostosis Clinic Populations with a Nonspecific Phenotype Tested for the p.Pro250Arg *FGFR3* Pathogenic Variant

Phenotype	p.Pro250Arg Variant Detection Frequency	References
"Apparently isolated" unilateral coronal synostosis	4%-12%	Moloney et al [1997], Reardon et al [1997], Gripp et al [1998], Renier et al [2000], Mulliken et al [2004]
"Apparently isolated" or "nonsyndromic" bilateral coronal synostosis	~30%-40%	Moloney et al [1997], Renier et al [2000]
Proband with coronal synostosis and positive family history [1]	9%-70%	Reardon et al [1997], Renier et al [2000]

1. FGFR1 & *FGFR2* pathogenic variants excluded

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Muenke syndrome, the following evaluations are recommended:

- Assessment of suture involvement by skull radiographs or preferably 3D skull CT
- Assessment for hydrocephalus with brain CT or MRI
- Assessment for exposure keratopathy
- Hearing assessment
- Developmental assessment in children
- Ophthalmologic assessment including screening for strabismus and vision. Additionally, this assessment should include fundoscopy to assess for papilledema, a finding that is present when intracranial pressure (ICP) is increased.
- Consultation with a clinical geneticist and/or genetic counselor

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 age 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).

Newer approaches being performed include endoscopic strip craniectomy and posterior distraction (PD):

- Endoscopic strip craniectomy is typically performed before the affected child reaches age three months and has an overall long-term improved symmetry compared to traditional cranial vault remodeling and fronto-orbital advancement.

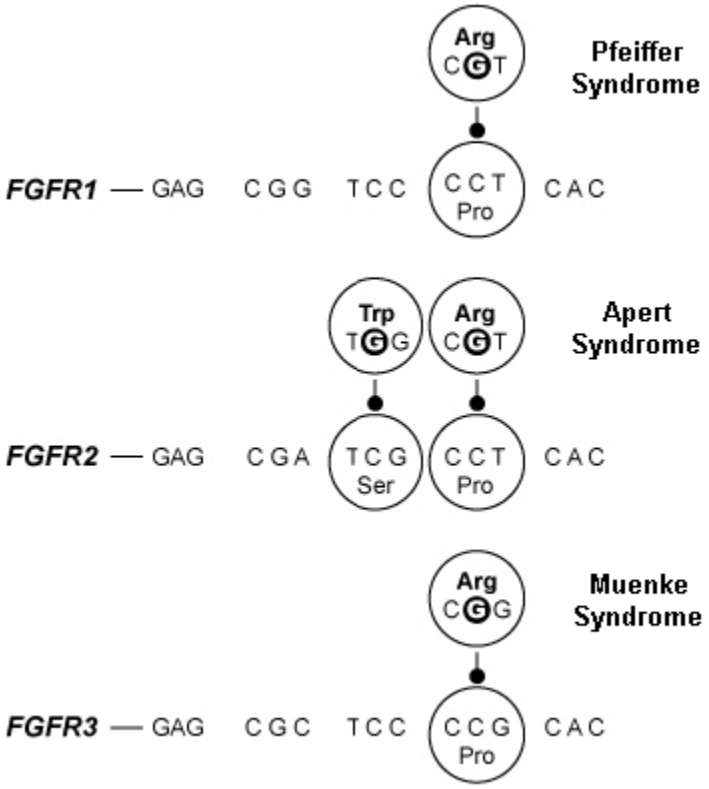

Figure 1. Diagram of the pathogenic C>G missense variants that result in a proline-to-arginine substitution at analogous positions in the protein products of *FGFR1*, *FGFR2*, and *FGFR3*

- Posterior distraction (PD) is used to manage individuals with severe brachycephaly or turribrachycephaly. The procedure has associated risks and more studies to establish long-term outcomes are needed [Wiberg et al 2012, Thomas et al 2014].

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:

- 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 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 the defining pathogenic variant for Muenke syndrome were more likely to require early intervention with a posterior release operation (at age ~6 months) to prevent excess frontal bulging than were those without the defining pathogenic variant.
  - Seven (24.1%) of 29 individuals 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; 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 do 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 delay. Individuals with Muenke syndrome are at increased risk for behavioral problems, intellectual disability, and developmental delay [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.

Prevention of Secondary Complications

Early surgical reconstruction for craniosynostosis may reduce the risk for complications including sequelae related to increased intracranial pressure (e.g., behavioral changes).

Surveillance

The following are appropriate:

- Regular developmental assessments of affected children
- Periodic repeat audiograms
- Periodic assessment for strabismus
- As part of protocol-driven care and management: annual multidisciplinary reviews and periodic review by a social work team. Protocol-driven approaches to surveillance currently in use include those of Flapper et al [2009] and de Jong et al [2010].

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 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, 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. —ED.

Mode of Inheritance

Muenke syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with Muenke syndrome have an affected parent.
- A proband with Muenke syndrome may have the disorder as the result of *de novo* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown.
- As in achondroplasia, *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.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include: physical examination; radiographs of the skull, hands, and feet; and testing for the *FGFR3* p.Pro250Arg pathogenic variant. 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 cannot be detected in the leukocyte DNA of either parent, possible explanations include *de novo* occurrence of pathogenic variant in the proband or germline mosaicism in a parent. Though theoretically possible, no instances of germline mosaicism have been reported.
- Note: Although most individuals diagnosed with Muenke syndrome have an affected parent, the family history may appear to be negative because of subtle/absent clinical findings (reduced penetrance) or failure to recognize the disorder in family members.

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 or has the defining *FGFR3* p.Pro250Arg pathogenic variant, the risk to the sibs of inheriting this pathogenic variant is 50%. Because penetrance is reduced and the phenotype is variable within a family, some individuals who inherit the *FGFR3* p.Pro250Arg pathogenic variant have no (or extremely mild) signs of Muenke syndrome.
- When the parents are clinically unaffected and do not have the *FGFR3* p.Pro250Arg pathogenic variant, the risk to the sibs is low.
- If the defining pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is presumed to be slightly greater than that of the general population (though still <1%) because of the theoretic possibility of parental germline mosaicism [Rannan-Eliya et al 2004].

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 is affected and/or has the *FGFR3* p.Pro250Arg pathogenic variant, his or her 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 parents. Uni- and bilateral coronal synostosis as well as absence of synostosis may be seen in individuals in the same family.

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

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Molecular genetic testing. Once the *FGFR3* p.Pro250Arg pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis 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. Molecular diagnosis of Muenke syndrome was made after birth in both twins.

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

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.

- **National Library of Medicine Genetics Home Reference**
  Muenke syndrome
- **Children's Craniofacial Association (CCA)**
  13140 Coit Road
  Suite 517
  Dallas TX 75240
  Phone: 800-535-3643 (toll-free)
  Email: contactCCA@ccakids.com
  www.ccakids.org
- **Face Equality International**
  United Kingdom
  Email: info@faceequalityinternational.org
  www.faceequalityinternational.org
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  PO Box 5801
  Bethesda MD 20824

Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
Craniosynostosis Information Page

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

Gene structure. Human *FGFR3* is 16.7 kb long and is composed of 17 coding exons [Perez-Castro et al 1997]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The amino acid p.Pro250 is located in the linker region between the second and third immunoglobulin domains of *FGFR3* (Figure 2). The c.749C>G (p.Pro250Arg) substitution in *FGFR3* is estimated to occur at a rate of $7.6\text{-}8 \times 10^{-6}$ per haploid genome, one of the highest known mutation rates for a transversion [Moloney et al 1997, Rannan-Eliya et al 2004].

Table 5. *FGFR3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.749C>G	p.Pro250Arg	NM_000142.4 NP_000133.1
c.749C>T [1]	p.Pro250Leu [1]	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. It is unclear if this pathogenic variant results in Muenke syndrome (see Genetically Related Disorders).

Normal gene product. The 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 in order 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 CNS [Robin 1999]. It is also present

in the skeletal precursors for all bones during the period of endochondral ossification and resting cartilage [Robin 1999].

Abnormal gene product. 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 (Figure 2) [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].

Animal models. *Fgfr3* knockout mice have elongated tails and hind limbs, implying that FGFR3 has a role in slowing skeletal growth [Robin 1999] and indicating that *FGFR3* pathogenic variants are hypermorphic, causing the mutated gene product to over-perform its normal function.

Figure 2. 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].

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.

Cohen MM Jr, MacLean RE. Anatomic, genetic, nosologic, diagnostic, and psychosocial considerations. In: Cohen MM Jr, MacLean RE, eds. *Craniosynostosis: Diagnosis, Evaluation, and Management.* New York, NY: Oxford University Press; 2000:119-43.

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, Maliepaard M, Bannink N, Raat H, Mathijssen IM. Health-related problems and quality of life in patients with syndromic and complex craniosynostosis. Childs Nerv Syst. 2012;28:879–82. PubMed PMID: 22234545.

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

de Jong T, Toll MS, de Gier HH, Mathijssen IM. Audiological profile of children and young adults with syndromic and complex craniosynostosis. Arch Otolaryngol Head Neck Surg. 2011b;137:775–8. PubMed PMID: 21844411.

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.

Doherty ES, Lacbawan F, Hadley DW, Brewer C, Zalewski C, Kim HJ, Solomon B, Rosenbaum K, Domingo DL, Hart TC, Brooks BP, Immken L, Lowry RB, Kimonis V, Shanske AL, Jehee FS, Bueno MR, Knightly C, McDonald-McGinn D, Zackai EH, Muenke M. Muenke syndrome (FGFR3-related craniosynostosis): expansion of the phenotype and review of the literature. Am J Med Genet A. 2007;143A:3204–15. PubMed PMID: 18000976.

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.

Graham JM Jr, Braddock SR, Mortier GR, Lachman R, Van Dop C, Jabs EW. Syndrome of coronal craniosynostosis with brachydactyly and carpal/tarsal coalition due to Pro250Arg mutation in FGFR3 gene. Am J Med Genet. 1998;77:322–9. PubMed PMID: 9600744.

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

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 PMID: 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;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.

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 PMID: 16251895.

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. The craniofacial surgeon as amateur geneticist. J Craniofac Surg. 2002;13:3–17. PubMed PMID: 11886985.

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 PMID: 15253176.

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.

Perez-Castro AV, Wilson J, Altherr MR. Genomic organization of the human fibroblast growth factor receptor 3 (FGFR3) gene and comparative sequence analysis with the mouse Fgfr3 gene. Genomics. 1997;41:10–6. PubMed PMID: 9126476.

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.

Reardon W, Wilkes D, Rutland P, Pulleyn LJ, Malcolm S, Dean JC, Evans RD, Jones BM, Hayward R, Hall CM, Nevin NC, Baraister M, Winter RM. Craniosynostosis associated with FGFR3 pro250arg mutation results in a range of clinical presentations including unisutural sporadic craniosynostosis. J Med Genet. 1997;34:632–6. PubMed PMID: 9279753.

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.

Sabatino G, Di Rocco F, Zampino G, Tamburrini G, Caldarelli M, Di Rocco C. Muenke syndrome. Childs Nerv Syst. 2004;20:297–301. PubMed PMID: 14963686.

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.

Solomon BD, Muenke M. Muenke syndrome. In: Muenke M, Kress W, Collman H, Solomon BD, eds. *Monographs in Human Genetics. Craniosynostoses: Molecular Genetics, Principles of Diagnosis and Treatment.* Vol 19. Basel, Switzerland: Karger Publishing; 2010:89-97.

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.

Chapter Notes

Author Notes

We have ongoing studies at the National Institutes of Health (NIH) that focus on various aspects of Muenke syndrome, and we hope to improve our understanding of hearing, cognitive function, and development in people with Muenke syndrome.

We are currently conducting research on the relationship between development, cognitive function, and hearing in individuals with Muenke syndrome. The goal of this study is to better understand the development of the central nervous system as well as to understand the causes of developmental delay and intellectual disabilities that can occur in some individuals with Muenke syndrome. This study will also help us to learn much about the long-term outcomes and functioning of adults with Muenke syndrome. In addition, we also hope to be able to outline factors that may contribute to and predict mental prognosis in individuals with Muenke syndrome. *Please note: You do not need to have developmental delay, intellectual disabilities, or hearing loss in order to participate in our study.*

Acknowledgments

We are indebted to the affected individuals we work with and their families. This work was supported by the Division of Intramural Research, National Human Genome Research Institute, National Institutes of Health.

Revision History

- 10 November 2016 (ma) Comprehensive update posted live
- 19 June 2014 (me) Comprehensive update posted live
- 7 December 2010 (me) Comprehensive update posted live
- 10 May 2006 (me) Review posted live
- 30 January 2006 (mm) Original submission

License