MUENKE SYNDROME

Otherwise known as?

Muenke syndrome is a rare genetic condition primarily characterized by craniosynostosis (premature fusion of the skull bones) and other related features. While Muenke syndrome is the most commonly used name, there are a few alternative names that are sometimes used to describe the condition:

1. Craniosynostosis, Muenke Type – This name highlights the primary feature of the condition, which is craniosynostosis, specifically of the type associated with Muenke syndrome.

2.FGFR3-related Craniosynostosis Syndrome – Muenke syndrome is caused by mutations in the FGFR3 gene (Fibroblast Growth Factor Receptor 3). This name emphasizes the genetic cause of the syndrome.

3. Muenke Craniosynostosis Syndrome – This is another variation used to describe the condition, often emphasizing the cranial differences as the main characteristic.

Despite these variations, Muenke syndrome is by far the most widely accepted and recognized name for the condition.

Signs & Symptoms

Muenke syndrome is a genetic condition caused by mutations in the FGFR3 gene, which can lead to craniosynostosis (the premature fusion of skull bones) and other associated features. The symptoms and signs of Muenke syndrome can vary significantly between individuals, but the condition typically includes a combination of craniofacial differences and other systemic manifestations.

1. Craniosynostosis

- Premature Fusion of Skull Bones: The most prominent feature of Muenke syndrome is craniosynostosis, the early fusion of one or more sutures in the skull. This can result in differing head shapes, such as:
  - Brachycephaly (short, broad head) due to premature fusion of the coronal suture.
  - Scaphocephaly (long, narrow head) due to premature fusion of the sagittal suture.
- Fontanelles (soft spots on the skull) may close prematurely, affecting the overall skull shape.

(continued overleaf)

Craniofacial Australia
204 Melbourne Street
North Adelaide
South Australia, 5006

W: craniofacial.com.au
E: familysupport@acmff.org.au
P: (08) 8267 4128

2. Facial differences

- Flattened Forehead: Due to craniosynostosis, children with Muenke syndrome often have a flattened or different forehead shape.
- Wide Eyes (Hypertelorism): The distance between the eyes may be wider than normal.
- Beaked Nose: The nose may have a distinct, pointed appearance, often referred to as a beaked nose.
- Protruding or Low-set Ears: The ears may have an unusual shape or position, often being lower-set or protruding slightly from the head.

3. Hearing Loss

- Conductive Hearing Loss: Some individuals with Muenke syndrome may experience hearing loss, usually conductive in nature. This type of hearing loss results from problems with the outer or middle ear structures, which can be related to differences in the ear or craniofacial structure.
- Decreased Hearing Sensitivity: Hearing loss may range from mild to moderate and can often be managed with hearing aids or medical interventions.

4. Intellectual and Developmental Delays

- Cognitive Impairment: While most individuals with Muenke syndrome have normal intelligence, some may experience mild cognitive delays or learning difficulties. These delays may be related to the craniofacial differences, but many individuals develop normally with early intervention.
- Speech Delays: Delayed speech development is common, which may require speech therapy.

5. Skeletal differences

- Short Stature: Some individuals with Muenke syndrome may have short stature compared to their peers. This could be due to mild skeletal differences or growth issues.
- Syndactyly: Some individuals may have syndactyly, which is the fusion of fingers or toes.

6. Neurodevelopmental Issues

- Motor Skill Delays: Children with Muenke syndrome may experience delays in motor skills, such as sitting, crawling, or walking, though they often catch up with therapy and support.
- Attention and Behavioural Problems: There may be behavioural or attention difficulties that require additional support, although they are not present in all individuals.

(continued overleaf)

Craniofacial Australia

204 Melbourne Street
North Adelaide
South Australia, 5006

W: craniofacial.com.au
E: familysupport@acmff.org.au
P: (08) 8267 4128

7. Other Possible Features

- Mild Cognitive Impairment: Most individuals with Muenke syndrome have normal intelligence, but some may experience mild cognitive or learning challenges.
- Cleft Palate or Lip: In rare cases, individuals with Muenke syndrome may have a cleft palate or cleft lip, though this is less common.

Causes

Muenke syndrome is a genetic condition caused by a mutation in the FGFR3 (Fibroblast Growth Factor Receptor 3) gene. This mutation affects skull development and leads to craniosynostosis (premature fusion of skull bones), as well as other characteristic features of the syndrome.

1. Genetic Cause

- FGFR3 Gene Mutation: Muenke syndrome is specifically caused by a mutation in the FGFR3 gene, which plays a crucial role in bone growth and development.
- Pro250Arg Mutation (P250R): The most common mutation associated with Muenke syndrome is a single amino acid change—proline is replaced by arginine at position 250 in the FGFR3 protein.
- This mutation leads to impaired signalling in the FGFR3 pathway, affecting the development of skull bones, and in some cases, other parts of the skeleton and nervous system.

2. Inheritance Pattern

- Autosomal Dominant Inheritance: Muenke syndrome follows an autosomal dominant pattern, meaning that only one copy of the mutated FGFR3 gene (from either parent) is enough to cause the condition.
- De Novo (New) Mutations: While Muenke syndrome can be inherited from an affected parent, it often occurs due to a spontaneous (de novo) mutation in individuals with no family history of the condition.

3. Effects of the Mutation

- Premature Skull Fusion (Craniosynostosis): The mutation causes impaired bone growth, leading to early closure of the skull sutures, which affects skull shape.
- Hearing Impairment: FGFR3 gene mutations can also impact inner and middle ear development, leading to hearing loss.
- Variable Symptoms: The severity and symptoms of Muenke syndrome can vary, even among affected family members.

(continued overleaf)

Craniofacial Australia

204 Melbourne Street
North Adelaide
South Australia, 5006

W: craniofacial.com.au
E: familysupport@acmff.org.au
P: (08) 8267 4128

Testing & Diagnosis

The diagnosis of Muenke syndrome is based on a combination of clinical evaluation (physical examination of cranial and facial features) and genetic testing to confirm the presence of the FGFR3 mutation.

1. Clinical Evaluation

A doctor will assess physical signs and symptoms that suggest Muenke syndrome, including:

- Craniosynostosis (premature skull fusion) – particularly of the coronal suture, leading to brachycephaly (broad, short head shape).
- Facial differences – such as a flattened forehead, widely spaced eyes, or a beaked nose.
- Hearing impairment – common in affected individuals.
- Skeletal anomalies – such as limb differences or short stature.
- Developmental delays – in some cases, though intelligence is often normal.

If Muenke syndrome is suspected based on these features, further diagnostic tests are performed.

2. Imaging Tests

To assess craniosynostosis and other skeletal differences, doctors may use:

- X-rays – to evaluate skull shape and bone growth.
- CT scan (Computed Tomography) – provides detailed images of the skull to detect fused sutures.
- MRI (Magnetic Resonance Imaging) – may be used in rare cases to evaluate brain structures.

3. Genetic Testing (Definitive Diagnosis)

To confirm the diagnosis, genetic testing is performed to check for mutations in the FGFR3 gene.

- DNA Sequencing: A blood or saliva sample is collected, and genetic sequencing is used to detect the Pro250Arg (P250R) mutation in the FGFR3 gene.
- Targeted Mutation Analysis: Since Muenke syndrome is caused by a specific single mutation, targeted genetic testing is often sufficient instead of whole-genome sequencing.

4. Additional Tests (If Needed)

Depending on the individual's symptoms, other tests may include:

- Hearing tests (audiometry) – to check for conductive hearing loss.

(continued overleaf)

Craniofacial Australia

204 Melbourne Street
North Adelaide
South Australia, 5006

W: craniofacial.com.au
E: familysupport@acmff.org.au
P: (08) 8267 4128

- Developmental assessments – to evaluate cognitive and speech development.
- Orthopaedic evaluation – to check for limb anomalies or skeletal problems.

Treatment

There is no cure for Muenke syndrome, but treatment focuses on managing symptoms, addressing skull differences, and improving quality of life. A multidisciplinary team of specialists, including craniofacial surgeons, neurologists, geneticists, audiologists, and therapists, is often involved in treatment.

1. Surgical Treatment for Craniosynostosis

One of the main issues in Muenke syndrome is craniosynostosis (premature fusion of skull sutures). If needed, surgery is performed to:

- Address skull shape and allow for normal brain growth.
- Reduce intracranial pressure (if present).
- Improve facial symmetry and address appearance.

Surgical Options:

- Cranial vault reconstruction (preferably performed in the first half of the baby's first year when brain growth is at its most active) will help reshape the skull, and also normalise the face shape when the fused suture is on one side only.
- Endoscopic surgery (minimally invasive) may also be an option.

2. Hearing Management

- Hearing tests (audiometry) are important because some individuals with Muenke syndrome experience conductive hearing loss.
- Hearing aids or cochlear implants may be recommended for significant hearing impairment.
- Speech therapy can help address speech delays related to hearing loss.

3. Developmental and Cognitive Support

- Early intervention programs help children with potential developmental delays.
- Speech therapy is useful for those with speech or language difficulties.
- Educational support may be needed for children with learning challenges.

4. Physiotherapy and Occupational Therapy

- Physiotherapy can help with motor skill development if delays are present.
- Occupational therapy supports fine motor skills and daily activities, particularly if limb differences affect movement.

(continued overleaf)

Craniofacial Australia

204 Melbourne Street
North Adelaide
South Australia, 5006

W: craniofacial.com.au
E: familysupport@acmff.org.au
P: (08) 8267 4128

5. Management of Skeletal Anomalies

- Orthopaedic evaluation may be necessary if limb anomalies (e.g., syndactyly or short stature) are present.
- Surgery for limb anomalies may be considered in severe cases.

6. Psychological and Social Support

- Counselling and support groups can help individuals and families cope with social and emotional challenges.
- Self-esteem support is important for children dealing with facial differences or developmental delays.

7. Regular Follow-Up and Monitoring

- Routine check-ups with a craniofacial team to monitor skull and brain development.
- Ongoing hearing assessments help detect any progressive hearing loss.
- Growth and development monitoring ensures children receive necessary interventions as they grow.

Did you know?

In Australia, approximately 2 babies per 100,000 births are diagnosed with Muenke syndrome.*

Muenke syndrome is the most common form of craniosynostosis caused by a single gene mutation (FGFR3). However, it has a highly variable presentation, meaning some individuals have noticeable skull and facial differences, while others may have very mild or even no obvious symptoms. This variability can make diagnosis challenging, and some people may not even realize they have the condition until they have a child who inherits it.

References:

Reference: Junaid, M., Slack-Smith, L., Wong, K., Bourke, J., Baynam, G., Calache, H., & Leonard, H. (2022). Epidemiology of Rare Craniofacial Anomalies: Retrospective Western Australian Population Data Linkage Study. J Pediatr, 241, 162-172.e169. https://doi.org/10.1016/j.jpeds.2021.09.060

Craniofacial Australia

204 Melbourne Street
North Adelaide
South Australia, 5006

W: craniofacial.com.au
E: familysupport@acmff.org.au
P: (08) 8267 4128

How we can support you:

- Care packs
- Financial assistance
- Family support coordinator
- Connection to other families