MUENKE SYNDROME

Otherwise known as?

Muenke syndrome is sometimes also referred to as FGFR3-related craniosynostosis, reflecting the specific change in the FGFR3 gene and the craniosynostosis commonly associated with the condition.

However, Muenke syndrome is the preferred and most widely used name because craniosynostosis is only one of the possible features of the condition.

Signs & Symptoms

Muenke syndrome has a highly variable presentation. Individuals may experience different combinations of features, and the type and severity can vary considerably from one person to another, including among members of the same family.

Possible signs and symptoms are outlined below:

1. Craniosynostosis

Craniosynostosis is a common feature of Muenke syndrome and occurs when one or more of the skull sutures (the flexible joints between the bones of the skull) fuse earlier than expected. The coronal sutures, which run from each side of the skull towards the top of the head, are most often affected.

Fusion of both coronal sutures may result in a short, broad head shape known as brachycephaly, while fusion of one coronal suture may cause asymmetry of the forehead and face, known as anterior plagiocephaly. Other sutures, including the sagittal suture, which runs along the top of the skull from front to back, may occasionally be involved.

2. Facial differences

Facial and eye differences vary and may include forehead or facial asymmetry, widely spaced eyes, drooping upper eyelids, mild prominence of the eyes, a slightly flatter or more recessed middle part of the face, or strabismus, where the eyes do not point in the same direction. Rarely, cleft lip and/or palate may occur.

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Craniofacial Australia
204 Melbourne Street
North Adelaide
South Australia, 5006

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

3. Hearing loss

Hearing loss can occur in Muenke syndrome and may be:

- Sensorineural: involving the inner ear;
- Conductive: involving the outer or middle ear; or
- Mixed: involving both.

The type and severity of hearing loss can vary between individuals. Some people may also experience recurrent or persistent middle-ear problems.

4. Development, learning and behaviour

- Development and learning vary among people with Muenke syndrome. Some people have typical development and learning, while others may experience developmental delay, learning difficulties, intellectual disability, or differences in attention and behaviour.
- Speech and language delay is the most frequently reported developmental concern. Some children may also have delays in gross or fine motor skills. Gross motor skills involve larger movements, such as sitting and walking, while fine motor skills involve smaller, more precise hand movements.
- Early assessment can help identify any additional needs and guide appropriate therapy or educational support.

5. Limb, hand and foot differences

Most people with Muenke syndrome have hands and feet that appear typical and function normally. However, differences affecting the bones of the hands, wrists, feet or ankles are reported in around half of people with the condition.

These may include broad thumbs or great toes, shorter or curved fingers or toes, joined fingers or toes (syndactyly), or fusion of some wrist or foot bones.

Some differences are clearly visible, while others are more subtle and may only be identified on X-ray.

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Causes

Muenke syndrome is caused by a specific change in the FGFR3 (fibroblast growth factor receptor 3) gene. This change, known medically as c.749C>G (p.Pro250Arg), is a pathogenic variant - meaning a gene change known to cause the condition.

1. Genetic Cause

- FGFR3 gene: the FGFR3 gene provides instructions for a protein involved in regulating cell growth and bone development.
- Specific gene change: Muenke syndrome is defined by one particular change in the FGFR3 gene. This change replaces one small building block of the FGFR3 protein, called proline, with another called arginine. It is known as p.Pro250Arg or P250R.
- Effect of the change: This makes the FGFR3 protein more active than usual and affects normal development, including the development of bones and structures within the inner ear.

2. Inheritance Pattern

- Autosomal dominant inheritance means that a change in only one copy of the gene can cause the condition. Each child of a person with the specific FGFR3 gene change has a 50% chance of inheriting the change.
- Inherited or new gene change: The gene change may be inherited from a parent or may arise as a new change, known as a de novo gene change.

Testing & Diagnosis

Muenke syndrome may be suspected based on a person's clinical features, medical and family history, and imaging findings. Because its presentation varies considerably and can overlap with other craniosynostosis conditions, the diagnosis is confirmed through genetic testing.

1. Clinical evaluation

The clinical team may assess:

- skull and facial development;
- hearing and vision;
- development and learning;
- hand and foot differences; and
- relevant medical and family history.

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2. Imaging tests

Head imaging may be used to assess the skull sutures and skull shape, assist with treatment planning, and examine the brain and surrounding structures. It may also be used to investigate concerns such as hydrocephalus (a build-up of fluid within spaces in the brain), or raised intracranial pressure – meaning increased pressure within the skull.

Depending on the person's age and clinical needs, imaging may include:

- ultrasound or skull X-rays to assess the skull sutures;
- computed tomography (CT) scans to provide detailed images of the skull, fused sutures and surrounding structures; or
- magnetic resonance imaging (MRI) scans to assess the brain and other structures within the skull.

Imaging may also be used to assess hand or foot differences, where clinically indicated. The clinical team will determine which type of imaging is most appropriate.

3. Genetic testing

Muenke syndrome is confirmed by identifying the specific c.749C>G (p.Pro250Arg) change in the FGFR3 gene. Genetic testing usually uses a blood or saliva sample.

Depending on the person's clinical presentation and family history, testing may involve sequencing the FGFR3 gene, which means reading its genetic code, or using a multigene panel that examines several genes associated with craniosynostosis.

4. Further assessments

Following diagnosis, further assessments may be recommended to identify any additional health, developmental or support needs. These may include:

- Audiology assessment to identify and monitor any hearing loss, with referral to an ear, nose and throat specialist where recurrent or persistent middle-ear problems are present;
- Developmental assessment covering areas such as motor skills, learning, behaviour, and speech and language;

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- Vision and ophthalmology assessment to identify any eye or vision concerns; and
- Assessment of hand or foot differences, where clinically indicated.

The clinical team will advise which assessments are appropriate for each individual.

Treatment

Treatment and support for Muenke syndrome are tailored to each person's needs and may change over time. Care is often coordinated through a multidisciplinary craniofacial team and may involve craniofacial surgeons, neurosurgeons, genetics specialists, audiologists, ear, nose and throat specialists, ophthalmologists, developmental specialists and allied health professionals, such as psychologists and social workers.

1. Surgical treatment for craniosynostosis

Where craniosynostosis is present, surgery may be recommended to:

- provide space for healthy skull and brain growth;
- prevent or relieve raised pressure within the skull; and
- improve skull and facial shape or symmetry.

The type and timing of surgery will depend on the sutures involved, the child's age, the shape of the skull, any associated clinical concerns and the child's individual needs.

Surgical approaches may include:

- Open cranial vault reconstruction or remodelling, in which sections of the skull are repositioned to create space and improve skull shape. This may include fronto-orbital advancement, where the forehead and upper parts of the eye sockets are moved forward;
- Minimally invasive suture-release surgery, such as endoscopic strip craniectomy, in which a narrow strip of bone is removed along the fused suture through small incisions; or
- Distraction osteogenesis, in which sections of bone are gradually moved apart using specially placed devices. This may include posterior vault distraction, which creates additional space at the back of the skull.

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The specific technique may vary between craniofacial teams and surgeons. Some children may require more than one operation over time, depending on their individual needs and how their skull and facial structures develop as they grow.

In the more obvious cases, particularly when the coronal suture is fused on one side, the distorted skull causes a distorted face as growth proceeds. This can be minimised by early surgery on the skull, ultimately requiring little or no facial surgery when growth is complete.

2. Hearing management

- Regular hearing assessments are recommended to identify and monitor any hearing loss over time.
- Ongoing care may involve an audiologist and, where middle-ear problems are present, an ear, nose and throat (ENT) specialist.
- Depending on the type and severity of hearing loss, support may include hearing aids, cochlear implants (electronic devices that can provide access to sound for some people with severe hearing loss) or other appropriate interventions.
- Speech and language support may also be helpful where hearing loss affects communication or development.

3. Eye and vision management

Regular ophthalmology assessments may be recommended to identify and manage eye or vision concerns. Depending on the individual's needs, management may include glasses or other vision support, treatment for strabismus, or treatment to protect the surface of the eye where dryness or exposure occurs.

4. Other specialist care

Some people with Muenke syndrome may require additional specialist care according to their individual features and needs. This may include:

- Neurological assessment and treatment where seizures or other neurological concerns are present;
- Dental, orthodontic or cleft-related care where relevant; and
- Genetic counselling to discuss inheritance, genetic testing within the family or future family planning.

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Other referrals or treatments may be recommended where an individual feature affects health, comfort or everyday functioning.

5. Developmental, learning and allied health support

Children with Muenke syndrome may benefit from developmental assessment and early intervention where additional needs are identified. Support will depend on the individual and may include:

- Speech pathology for speech, language, communication or feeding difficulties;
- Physiotherapy to support movement and gross motor development;
- Occupational therapy to support fine motor skills, sensory processing needs (such as responses to sound, touch or movement), and participation in everyday activities;
- Support for hand or foot differences, where these affect movement, comfort or participation in everyday activities;
- Psychological support relating to emotional wellbeing, treatment experiences, appearance concerns, self-confidence or social experiences;
- Social work support to help individuals and families access services, practical assistance and community supports;
- Educational support or adjustments for children experiencing learning difficulties; and
- Peer support, including opportunities to connect with other individuals or families with similar experiences.

The type and level of support required may change over time.

6. Ongoing follow-up

Long-term follow-up with a multidisciplinary team is an important part of care for people with Muenke syndrome.

Different specialists may be involved at different stages, depending on the person's clinical features, previous treatment and changing needs as they grow.

Ongoing follow-up allows existing concerns to be monitored, new needs to be identified, and treatment or support to be adjusted over time.

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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.

Did you know?

A Western Australian population study reported a birth prevalence of approximately 2 babies with Muenke syndrome per 100,000 births.*

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

MUENKE REFERENCE ---Review of literature 2007 American Jnl of medical genetics Part A

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