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# Headlines

## Craniofacial Support



# Muenke Syndrome

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# MUENKE SYNDROME INFORMATION SHEET

## What is Muenke syndrome?

Muenke syndrome is named after Max Muenke, a Genetics doctor who originated from Germany but currently practices in the United States. Dr. Muenke led the team that discovered this condition in 1996. Some people are reluctant to see one person's name associated with a discovery that resulted from a team effort, so you may see it referred to by various other terms such as "FGFR3-associated coronal synostosis", "Pro250Arg" or "The P250R mutation".

## How was Muenke syndrome identified?

To understand how Muenke syndrome was identified, you need to know how doctors usually recognise and describe new medical conditions. This generally involves identifying a recurrent pattern of signs (physical features of a person), and symptoms (what problem the person complains of), often backed up by the results of specific tests (for example, blood tests and X-rays). Craniosynostosis syndromes such as those with the names of Apert, Crouzon, Pfeiffer and Saethre-Chotzen, were recognised by doctors over 40 years ago, based on characteristic physical features.

Muenke syndrome was *not* recognised in this fashion, because the physical features are not very characteristic. Instead, it is defined by the result of a specific genetic blood test. Such tests only became possible in the mid-1990's, when the genetic alterations that cause some of the craniosynostosis syndromes began to be discovered. Dr. Muenke's group found that a specific chemical change in one of the genetic instructions (genes) termed FGFR3, was frequent in people with craniosynostosis affecting the coronal sutures. (FGFR3 is short for "fibroblast growth factor receptor type 3"). The change is at position 250 of the protein that is encoded by the gene.

Muenke M, et al (1997) A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) defines a new craniosynostosis syndrome.

American Journal of Human Genetics 60:555-564

*Documents the physical features of Muenke syndrome with photographs and X-rays*

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## Bibliography

Some of the most important papers published on Muenke syndrome are listed below. Headlines – Craniofacial Support has a complete list of publications available.

Bellus GA, et al. (1996). Identical mutations in three different fibroblast growth factor receptor genes in autosomal dominant craniosynostosis syndromes. *Nature Genetics* 14:174-176.

*The first identification of the Pro250Arg mutation in FGFR3.*

Cohen, MM Jr FGFR3-associated coronal synostosis syndrome (Muenke craniosynostosis). In: Cohen, MM Jr and MacLean RE (2000).

*Craniosynostosis. Diagnosis, evaluation and management*, Chapter 23. Oxford, Oxford University Press.

*A useful general overview.*

Lajeunie E, et al. (1999). Sex related expressivity of the phenotype in coronal craniosynostosis caused by the recurrent P250R FGFR3 mutation. *Journal of Medical Genetics* 36:9-13.

*Contains data suggesting that girls tend to be more severely affected than boys, on average.*

Moloney DM, et al. (1997). Prevalence of Pro250Arg mutation of fibroblast growth factor receptor 3 in coronal craniosynostosis. *Lancet* 349:1059-1062.

*This survey highlighted the high frequency of Muenke syndrome.*

The protein is altered so that a chemical called “arginine” replaces a chemical called “proline” at this specific position (hence the terminology Pro250Arg or P250R).

Muenke syndrome differs from other craniosynostosis syndromes in that it is defined by a positive result for this genetic test, rather than characteristic physical features. In fact, individuals who, it is now realised, have this condition previously had a wide variety of diagnostic “labels” attached to them, which we now know were incorrect. A partial list of such labels includes Crouzon, Pfeiffer and Saethre-Chotzen syndromes, and non-syndromic craniosynostosis. Indeed, the existence of Muenke syndrome is still not widely known by many doctors, so children with Muenke syndrome are sometimes still mistakenly given one of these other labels.

### **What are the physical features of Muenke syndrome?**

The diagnosis of Muenke syndrome is usually initially made because of craniosynostosis affecting the coronal sutures (the sutures that cross the head from ear to ear). This may affect only one side (unicoronal synostosis) or both sides (bicoronal synostosis). Apart from the resulting distortion in skull shape, the appearance is otherwise essentially normal. There are no other physical features that are characteristic of the diagnosis, although the fingers may sometimes be short, slightly crooked or webbed, but this does not affect their function. It has been estimated that about 1 in 20 people with unicoronal synostosis, and up to 3 in 10 people with bicoronal synostosis, have Muenke syndrome. It seems that the coronal sutures are rather specifically involved, so if your child has isolated synostosis of the midline sutures (metopic or sagittal), they are unlikely to have Muenke syndrome. However, some people (about one quarter in published studies) with Muenke syndrome do not have craniosynostosis at all – some have a large head size only and others have essentially normal skulls.

Work by the Paris group has suggested that Muenke syndrome is more severe, on average, in girls than in boys. 70% of girls with the mutation had bicoronal synostosis and only 10% had no significant craniosynostosis, whereas the corresponding figures for boys were 35% and 30% respectively. Nevertheless, in the individual case there is considerable overlap between the sexes.

It has also been shown that the overall outcome of surgery is somewhat less favourable, with a higher chance of needing a repeat operation, in Muenke syndrome than in other cases of “non-syndromic” coronal synostosis – so it is important not to miss appointments with the craniofacial specialist.

### Are there other implications of Muenke syndrome?

Apart from craniosynostosis, it has been suggested that hearing loss and learning difficulties are more common in Muenke syndrome. It is important for affected individuals to have hearing tests to check on the possibility of a problem. The chance of learning problems has been estimated at between 10 and 30%; the true figure is probably at the lower end of this range, as more severely affected children are more likely to come to medical attention. The table below summarises the frequency of the major features of Muenke syndrome. Note that growth in this condition is nearly always within the normal range.

Physical features of Muenke syndrome, based on published studies			Frequency (%)
<b>SKULL:</b>	Craniosynostosis:	Bicoronal	50
		Unicoronal	20
	Macrocephaly (large head)		5
	No significant skull problem		25
<b>LIMBS:</b>	Minor digit problems	(slightly short, crooked or webbed)	50
<b>HEARING:</b>	Significant hearing loss		30
<b>MENTAL:</b>	Mild-moderate learning difficulties		20
<b>GROWTH:</b>	Short stature		Less than 5

### How is Muenke syndrome inherited?

Our genes occur in pairs, and in Muenke syndrome, one FGFR3 gene is altered (mutated) and the other is normal. A person with Muenke syndrome will pass only one or other gene to each child, so the risk for each child to inherit the condition is 1 in 2 or 50:50. In the case of apparently healthy parents who have a child with Muenke syndrome, it is important for the parents themselves to be tested in case one of them is themselves a carrier. If the test is positive in one of the parents, the risk for further children is again 50:50, but if it is negative, the risk is likely to be much lower, under 1 in 100, as the child’s condition has arisen as a “new mutation”. It is essential to discuss the results and interpretation of any genetic testing with a clinical geneticist.

### How common is Muenke syndrome?

Muenke syndrome is probably the commonest of the currently recognised craniosynostosis syndromes. Although no accurate measurement of its birth prevalence has been published, 1 in 30,000 would be a reasonable estimate. This would make it about twice as common as Apert, Crouzon and Saethre-Chozen syndromes, and about three times as common as Pfeiffer syndrome.

### Why is a diagnosis of Muenke syndrome important?

The diagnosis is important for two reasons. First, the implications for the child’s health are different. Generally speaking, Muenke syndrome is milder in its consequences compared to other craniosynostosis syndromes; but somewhat more severe than in a simple, “non-syndromic” craniosynostosis. Second, a diagnosis of Muenke syndrome has genetic implications. This means that there is a chance that other family members may be affected. The risk can be accurately quantified and specific testing is possible.