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Headlines

Craniofacial Support



Craniofrontonasal Syndrome

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Further reading (technical and not necessarily easy to obtain!)

This report is the first recognition of CFNS as a distinct condition:
Cohen MM (1979). Craniofrontonasal dysplasia. Birth Defects XV(5B): 85-89.

This article reviews the clinical features of CFNS:
Cohen MM, Jr (2000). Craniofrontonasal syndrome. In: Craniosynostosis: Diagnosis, Evaluation and Management. Cohen MM Jr, MacLean RE (eds) Oxford University Press, Oxford, pp 380-384.

These two papers review what is known about EFNB1 (ephrinB1) mutations in CFNS:
Twigg SRF and Wilkie AOM (2007). EFNB1 and EFNA4 in craniofrontonasal syndrome and craniosynostosis. In: Inborn Errors of Development: The Molecular Basis of Clinical Disorders of Morphogenesis. Charles J. Epstein, Robert P. Erickson, and Anthony Wynshaw-Boris (eds) New York: Oxford University Press, (Publication pending).

Wieacker P, Wieland I (2005). Clinical and genetic aspects of craniofrontonasal syndrome: Towards resolving a genetic paradox. Mol Genet Metab 86:110-116

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What is craniofrontonasal syndrome?

Craniofrontonasal syndrome (CFNS) was first recognised as a distinct medical condition in 1979 by Professor Michael Cohen, a Medical Geneticist who works in Canada. Clinical descriptions of what we now know as CFNS date back to the 1920s and alternative names for the syndrome include craniofrontonasal dysplasia and craniofrontonasal dysostosis.

How common is CFNS?

CFNS is one of the rarer craniosynostosis syndromes that doctors currently recognise. There is no accurate measurement of its birth frequency, but an estimate derived from experience over 10 years at the Oxford Craniofacial Unit puts the figure at very approximately 1 in 120,000.

What are the physical features of CFNS?

CFNS in girls.

CFNS affects girls more frequently, and more severely, than boys (the reasons for this are discussed below). The diagnosis is usually initially made because of a combination of craniosynostosis affecting the coronal sutures (these are the sutures that run from one ear to the other across the top of the head), wide-spaced eyes (hypertelorism) and a shallow cleft in the end of the nose. Some girls have both coronal sutures affected (bicoronal synostosis), in others only one side is fused (unicoronal synostosis) and in some (~15%) craniosynostosis is absent. Hypertelorism and a broad nose are always present and the wide spaced eyes can often lead to the development of a squint (the eyes are not aligned properly) that needs to be treated early.

Other common features of CFNS include faint longitudinal splits in the nails, thick curly hair, mild hand and foot changes such as a curved 5th finger and skin webbing between the digits (cutaneous syndactyly), webbed neck, and sloping shoulders sometimes associated with restricted shoulder movement or breast underdevelopment. In a smaller proportion of cases, mild learning difficulties, cleft lip (sometimes with cleft palate), duplication of the thumbs or big toes, abnormalities in formation of the womb (uterus) and a gap in the muscle separating the chest and stomach (diaphragmatic hernia) may occur. There is currently no evidence that CFNS is associated with specific new health problems later in life such as heart disease, diabetes or cancer.

CFNS in boys.

Boys are usually much more mildly affected than girls with the most common feature being wide-spaced eyes (hypertelorism). Unless they are born into a known family affected with CFNS, or if they are the father of a girl affected with CFNS, it is unlikely that these males will have come to a doctor's attention. There is a very small subset of boys, however, who have the more severe features found in girls, but these cases are extremely rare.

The approximate frequency of different features of CFNS based on published studies in the medical literature, is shown in the table opposite (note that the table specifically omits inclusion of the very rare, more severely affected, males).

What causes CFNS?

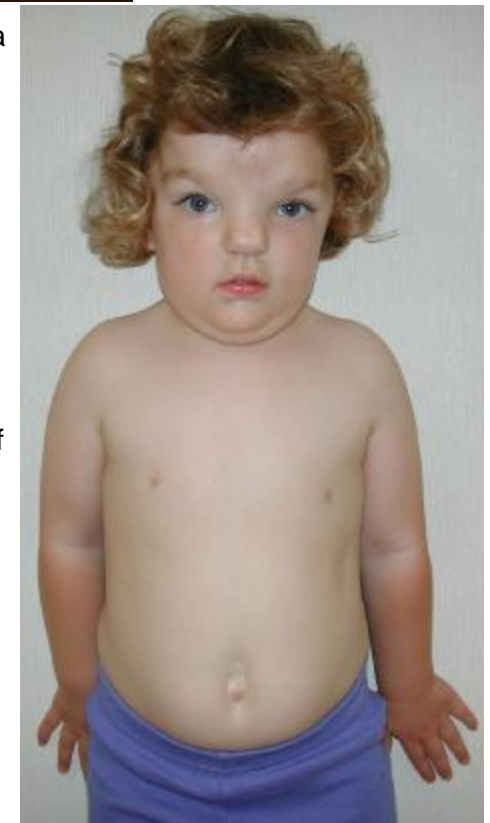
CFNS is caused by a chemical change in a person's set of genetic instructions (the DNA). The nature of this change was identified simultaneously in 2004 by two research groups (in Oxford, UK and Magdeburg, Germany). It occurs in a gene (one of the genetic instructions) called EFNB1, or EphrinB1. The vast majority of people with CFNS have changes that affect this gene. Importantly for understanding the next section, the EFNB1 gene lies on the X chromosome (this is a large piece of DNA that can be seen down the microscope, with many other genes besides EFNB1).

Why is CFNS more severe in girls?

The answer to this question is not straightforward or easy to understand (or explain!). Essentially it is because of a combination of where the CFNS gene is located on our chromosomes, and the way that the CFNS gene works in controlling the development of the body. CFNS is highly unusual in that girls are more severely affected than boys and this has long puzzled doctors. As mentioned above, the altered EFNB1 gene that causes CFNS lies on the X chromosome, one of the sex chromosomes (so called because girls have two X chromosomes, whereas boys have only one X chromosome, partnered with a different, Y chromosome). Usually, conditions caused by an altered gene on an X chromosome are more severe in boys than girls (a familiar example is red/green colour blindness). This is because in girls the presence of a second, *normal* X chromosome is usually sufficient to overcome the effects of the *abnormal* X



The longitudinal nail splits are a characteristic feature of CFNS



This girl has wide-spaced eyes, a flat forehead, broad nose with a shallow central groove, thick curly hair and asymmetric nipples, all of which can occur in this condition.

chromosomes, genes and mosaicism is given in the Headlines Leaflet No1: "What causes craniosynostosis? - a general discussion with a focus on genetic aspects (syndromes).

How is CFNS diagnosed and why is it important?

In girls, CFNS has characteristic physical features usually allowing doctors readily to distinguish this syndrome from related conditions. The diagnosis is often supported by X-rays and confirmed by a specific genetic blood test. This blood test looks for changes in the EFNB1 gene. A positive finding confirms the diagnosis of CFNS.

A diagnosis of CFNS in a girl does not directly affect the medical management of issues that may already be apparent such as craniosynostosis, wide-spaced eyes (hypertelorism) and squint. However, it may account for the physical features observed and alert doctors to look for other features that may be less readily apparent (see Table above). Problems with the eyes, such as a squint, can arise from the wide-spaced eyes and need to be addressed early on in the child's development. The craniosynostosis found in CFNS is no different to that seen in related syndromes, but each case needs to be individually assessed by an experienced craniofacial team.

A diagnosis of CFNS also has genetic implications, meaning that there is a chance of other members of the family being affected, particularly males who may appear normal. Specific testing is essential for accurate risk values to be calculated, as discussed in the previous section. When a genetic alteration (mutation) has been identified, and there is a chance of CFNS arising in future pregnancies, specific genetic testing of the pregnancy (prenatal diagnosis) may be possible, to determine whether the unborn child will be affected. Discussion of these complex issues with a clinical geneticist is essential.

Physical features of CFNS based on published studies		
(nd = not described)	Frequency (%)	
	Girls	Boys
Wide-spaced eyes (hypertelorism)	100	100
Coronal craniosynostosis – both sides	40	nd
Coronal craniosynostosis – one side	43	nd
Cleft lip	12	Can be present
Cleft palate	17	nd
Normal mental/motor development	67	100
Complete/partial absence of the corpus callosum (nerves connecting the two sides of the brain)	40	nd
Squint	81	Can be present
Neck/underarm webbing	27	nd
Limited shoulder movement	22	nd
Chest anomalies	35	Can be present
Extra finger	4	nd
Extra toe	12.5	nd
Minor hand changes (webbing, curved 5 th finger)	62	nd
Minor foot changes (webbing, broad toe)	47	nd
Grooved nails	90	Can be present
Thick, wiry hair	72	nd

chromosome. Strangely, in CFNS, the situation is reversed, with the presence of both the *normal* and *abnormal* X chromosomes in girls leading to a more severe outcome (see table next page).

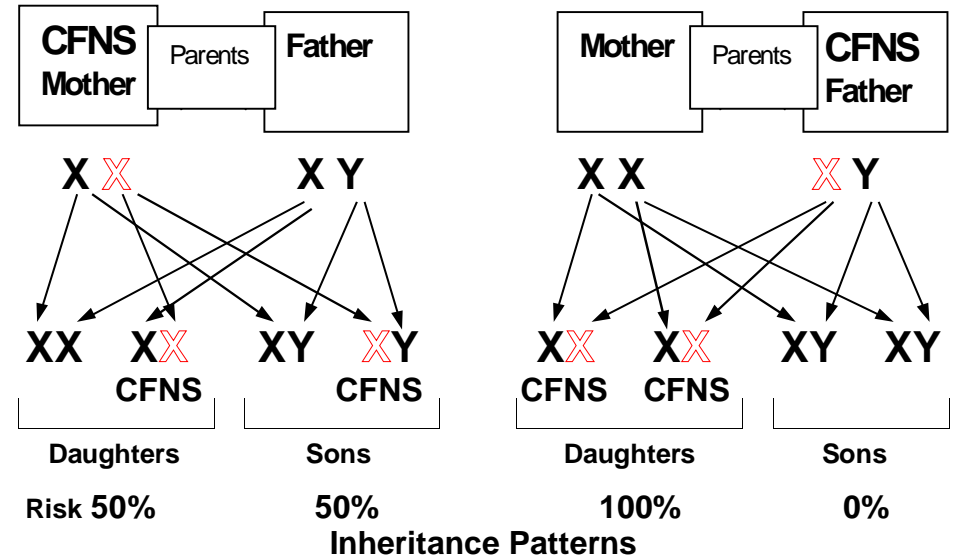
Females have two X chromosomes and males have one X and one Y (male specific) chromosome	Female	Male
	XX	XY
Usually an abnormal X results in more severely affected males	XX	XY affected
In CFNS, females are paradoxically more severely affected	XX affected	XY mild

The explanation of this paradox lies in a normal process called X-inactivation. In order that boys and girls have the same amount of ephrinB1 (which is important for it to work properly) one of the girls' X chromosomes is turned off. This "switching off" occurs randomly so in a girl with CFNS, her body tissues contain a mix of cells either with normal ephrinB1 or with abnormal ephrinB1. The function of ephrinB1 is important early in a baby's development for setting up "boundaries" between different tissues. Because both normal ephrinB1 and abnormal ephrinB1 are present in girls with CFNS, extra "boundaries" which shouldn't be there are set up between these groups of cells in the skull and other organs. As a result of this, the extra physical features seen in girls develop. In boys with the altered CFNS gene, who only have abnormal ephrinB1, no extra boundaries are set up and consequently their symptoms are much milder.

How is CFNS passed on to children?

If one of the parents is affected.

As already stated, the EFNB1 gene altered in CFNS resides on the X chromosome, two of which are present in girls and one in boys. A girl with CFNS would therefore have one abnormal X (with the altered gene) and one normal X, while a boy with CFNS would have a single abnormal X. Only one or other of the X chromosomes of the mother is passed on to her children. Therefore, the risk to a child (boy or a girl) of inheriting the CFNS gene from her mother is 50%. A father always passes on his X chromosome to his daughter(s) and never to his son(s). Therefore, the risk to a daughter of inheriting CFNS from her father is 100% while any sons will have no risk. These inheritance patterns are depicted opposite.



If neither parent is thought to be affected.

When apparently unaffected parents have a child with CFNS, it is important for the parents themselves to be tested in case one of them is a carrier, for example the father may be a mildly affected carrier previously unnoticed by doctors. If the test is positive in the father, the risks for further children are the same as outlined above. If the test is positive in the mother then *mosaicism* (see below for explanation) is possible and the risks to her subsequent children might be lower than 50%. If the test is negative in both parents the risk is likely to be lower as the child's condition may have arisen as a "new mutation" (a miscopy in either the egg or sperm that formed the child). However, some caution must be exercised when considering negative results in the parents. This is because a phenomenon called *mosaicism* can occur in CFNS in about 1 in 5 cases. *Mosaicism* arises when the genetic alteration occurs in the early embryo during development of the baby in the womb. Such an individual will carry a *mosaic* mix of cells, some with and some without the CFNS alteration. This person may appear quite normal, but if the CFNS cells contribute to the sperm or eggs, then the risk for the children of this person to have CFNS may be substantial. Given the complexity of the situation, it is extremely important to discuss the findings and interpretation of any genetic test with a clinical geneticist. A more detailed discussion of