

# **The Genetics of Microcephaly**

## **Introduction**

The term, microcephaly means 'small head'. Just like hat size, head size is assessed by measuring the head's maximum circumference - the occipito-frontal circumference or OFC.

Just as height may vary from person to person, individuals OFC measurements vary also. OFC measurements have been made across different populations and at different ages and charts are used to plot OFC growth in childhood. Different charts are available for boys and girls since males tend to have larger heads than females. One commonly employed definition of microcephaly is, after taking age and sex into account, an OFC measurement that is less than the range of OFC measurements present in over 99% of the entire population (an OFC greater than three standard deviations below the mean).

Reduction in OFC usually means that the volume of the brain is also reduced. More severe reductions in OFC have medical importance because the factors that cause reduced brain growth may cause mental and physical disabilities. Although some degree of disability usually accompanies microcephaly, disability is not an inevitable consequence.

Causes of microcephaly are listed below. Note that although different causes are known, many individuals are affected for no definite reason and the medical tests that they undergo fail to provide any clues as to the cause.

## **Some causes of microcephaly**

- Genetic chromosome disorders
- Genetic single gene disorders
- Certain prenatal infections affecting the fetus
- Cerebrovascular accident in the fetus (stroke)
- Severe birth asphyxia (prolonged lack of oxygen to the brain)
- Severe illness or infection such as meningitis or encephalitis in infancy
- Rarely, certain maternal illnesses

## **What do different causes of microcephaly have in common?**

The origins of microcephaly lie before birth or in the first year of life. During this period, the brain is growing very rapidly and any adverse factor such as a particular virus infection or a decrease in the brain's blood supply, may cause brain growth to irreversibly slow or cease.

Genetic factors also have their effect during the critical period of brain development. Some genetic conditions are associated with abnormal development of other parts of the body such as the eyes, the heart and the limbs. In these cases, microcephaly may only be one part of a medical 'syndrome'.

A definition of a syndrome is a recognisable pattern of abnormalities that occur together. Many named syndromes exist and parents of children who are affected by named syndromes often get help and information from a specific support group under the 'Contact a Family' umbrella.

Quite frequently, microcephaly is discovered in a child who comes to doctors' attention during the first years of life with delays in development. If the microcephaly is severe and all the child's blood tests and scans fail to provide an explanation, the parents may be told that it is likely their child has genetic microcephaly.

On the face of things, this is often difficult to understand, especially if routine genetic blood tests have given normal results and the family history gives no indication of underlying hereditary predisposition.

In fact, if there is only one child with microcephaly in the family, a genetic cause tends to be the diagnosis that doctors reach by excluding other known causes of microcephaly through blood tests and brain scans. Of course, in this situation, there may be a slight doubt about the true diagnosis.

In contrast, if there is more than one affected person in a family, or if a genetic blood test gives an abnormal result, it is possible to be more certain that genetic factors are important.

## **Genetics and Inheritance**

Some knowledge of genetics and inheritance is needed to understand origins of genetic microcephaly. Each body tissue is composed of billions of cells that carry the fundamental units of inheritance called genes. About 20,000 of these genes contain all the instructions required to make an individual and to keep him or her healthy.

Genes are too small to be visible but larger packages called 'chromosomes,' in which genes are located, can be seen down a microscope. Over 40 years ago it was discovered that each person has 23 pairs of chromosomes. Chromosomes come in pairs because one copy of each pair inherited from each parent. Thus, 23 chromosomes are passed on in the mother's egg and 23 chromosomes are also inherited in the father's sperm cell. Genes but it does harbour the specific genes necessary to instruct the developing embryo to become male

Note that a father produces two types of sperm: one will contain his Y chromosome and the other type carries his X chromosome. X and Y chromosome bearing sperm cells each have a 50:50 chance of fertilising the egg. If a Y-bearing sperm fertilises the mother's egg a son will be born; if an X-bearing sperm achieves fertilisation, a daughter will be born.

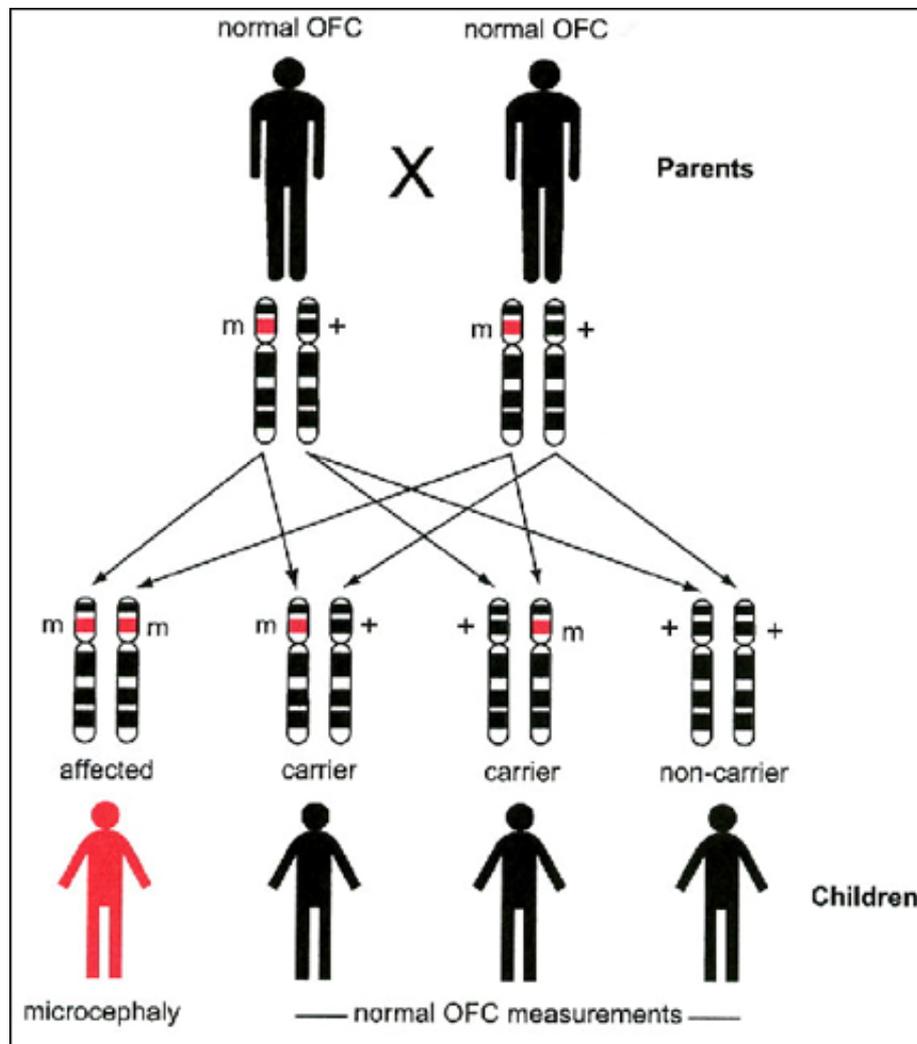
We know that any gene in the total of 20,000 may become damaged. Usually, this does not matter because, just like the chromosomes, genes come in pairs, one inherited from father and the other inherited from mother. When one gene is faulty, the second copy of that gene usually compensates for it.

However, males have a single X chromosome and only one copy of each gene that is located, is on this X chromosome. If a particular X chromosome gene is faulty, that will show up in the affected male. This explains why males are more liable to be affected by certain diseases or traits such as colour blindness that are caused by faults within genes located on their solitary X chromosome.

## **Different Types of Genetic Microcephaly**

Aside from microcephaly caused by major chromosome abnormalities such as Down's syndrome or smaller chromosome abnormalities such as Angelman syndrome, there are three main types of genetic microcephaly. These three types may be distinguished by recording details of the family history. In the first two types microcephaly affects males and females with equal likelihood (termed autosomal microcephaly) but in the third type males are affected (termed sex linked or X-chromosome linked microcephaly)

Autosomal recessive microcephaly This occurs when unaffected parents each pass on to their child a single copy of the same faulty gene. In both unaffected parents, the single faulty gene is compensated for by the second normal copy of that gene. Hence, the microcephaly gene is termed 'recessive'. But the child is affected because he or she has two faulty copies and no normal copies of the gene.

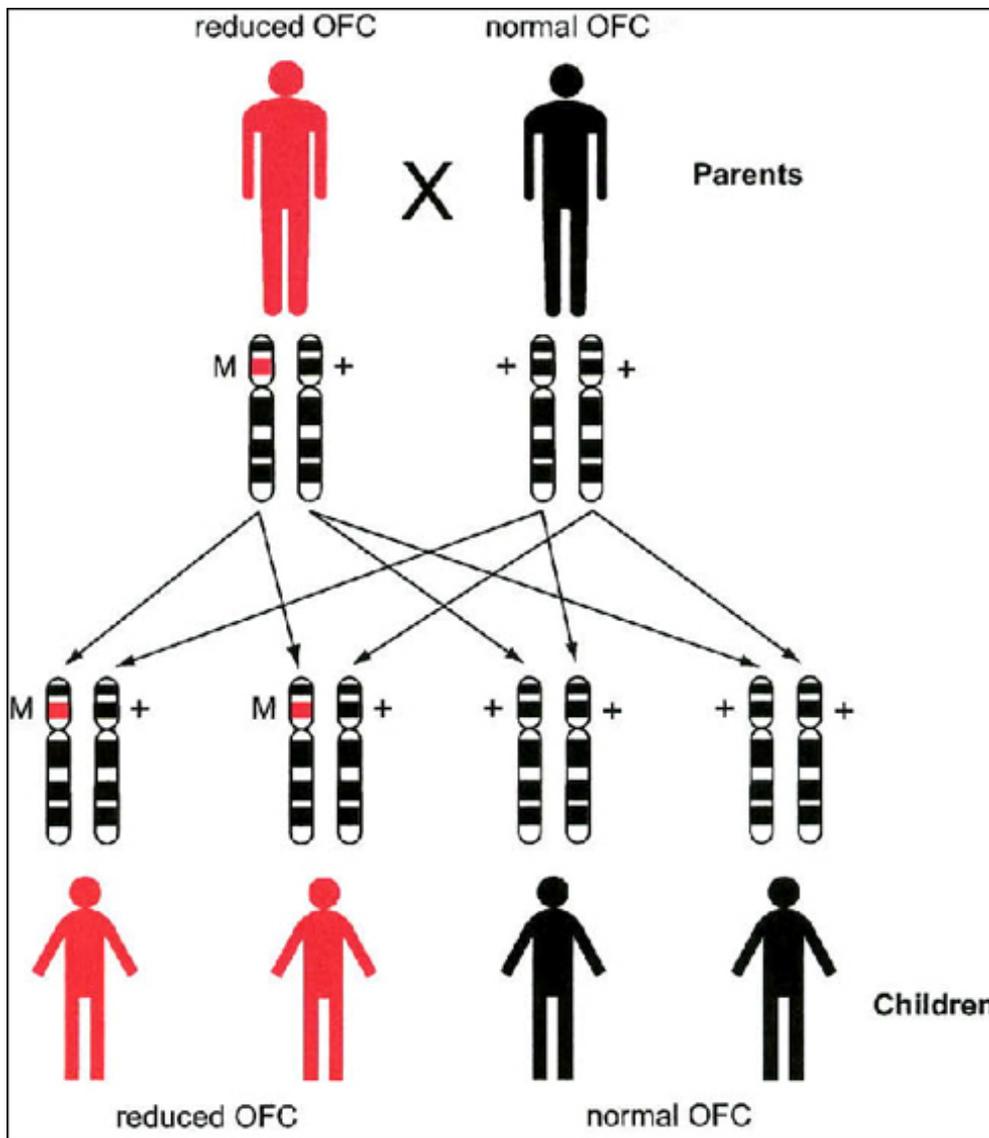


Usually, it is just by chance that partners carry the same faulty gene. However, if a couple are blood relatives and therefore share a proportion of their genes, there is a slightly increased chance that they will carry the same faulty genes.

If parents have one child with autosomal recessive microcephaly, the risk of recurrence in each subsequent pregnancy is 25%. Unaffected brothers and sisters of an affected person each have 66% chance of carrying a single

Each pair is distinct and the pairs are labelled from 1 to 22, with the 23rd pair being known as the sex chromosomes. In females, the sex chromosomes comprise 2 identical X chromosomes but males have a single X chromosome and a small Y chromosome. The Y chromosome does not carry microcephaly microcephaly gene inherited from one or other parent. But, for an affected child to be born, their partner would also need to carry and pass on the same gene. The chance of this happening is low.

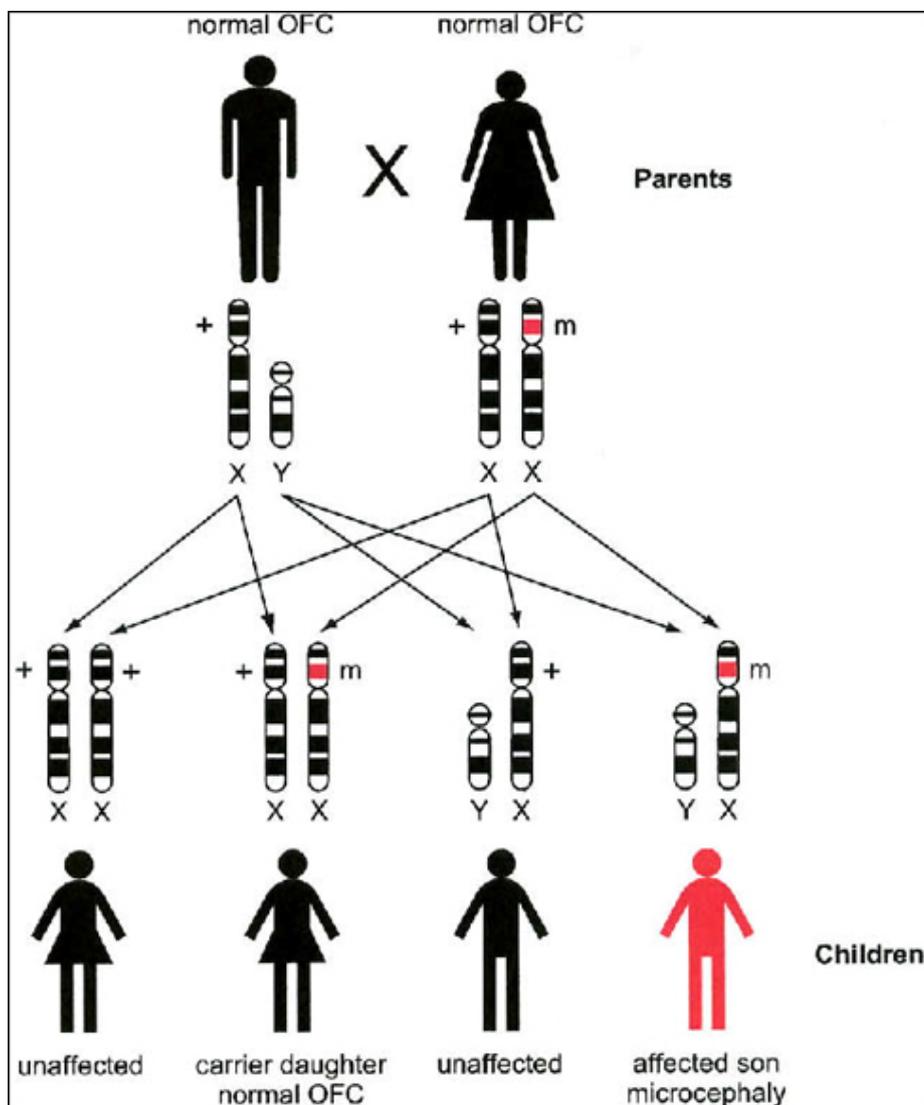
Autosomal Dominant Microcephaly. Here, in an affected person a single microcephaly gene over-rides or is 'dominant' over the second, normal copy of that gene. The chance of the affected person passing on a dominant microcephaly gene and having an affected child is therefore 50%.



Dominant microcephaly may be a mild condition and can vary from generation to generation. A family with several affected relatives may only come to medical attention if one of the relatives is more severely affected. It is only through measuring other relatives' OFC that microcephaly with minimal clinical effect is identified.

Sometimes, neither parent of an individual who has dominant microcephaly is themselves affected. A possible explanation for dominant microcephaly arising for the first time in a family is that the gene in question became faulty in one unaffected parent's egg or sperm cell. This phenomenon is called a new mutation.

X Chromosome linked microcephaly. This is the least common type of microcephaly. It is caused by a faulty gene located on the X chromosome and it is mainly males who are affected. Since the gene fault is recessive, females carrying the gene are usually unaffected.



There is a 50% chance that a son of a carrier female will be affected and a 50% chance that a daughter will be an unaffected carrier like her mother.

### New genetic tests for microcephaly

To understand genetic causes of microcephaly in more detail, research has concentrated on trying to locate and identify the specific gene faults that cause this condition. Recently, through detailed family studies that employ DNA tests, several different autosomal recessive microcephaly genes have been identified.

The genes that are now known to cause microcephaly have been given technical and short-hand names that include MCPH1, ASPM or MCPH5 and SLC25A19. Other genes that are located but not yet fully characterised. Many families have kindly assisted genetic microcephaly research but, unfortunately, not all families will have a type of genetic microcephaly that is diagnosable by gene-based tests during pregnancy or later in life. If this is the situation, parents may still ask what are the chances of a second child in their family having microcephaly? One affected child, all genetic test results negative

Occasionally, the geneticist may recognise a special types of genetic microcephaly from a clue in the extended family history, or a blood test result.

If there are no tests that pinpoint a specific gene fault, the geneticist may have to give advice to the family that is based upon his or her cumulative experience.

From past experience, it suspected that if all known causes of microcephaly such as prenatal infections or prenatal strokes and chromosome disorders can be ruled out, about half of all children with microcephaly and no history of an affected relative, are affected by autosomal recessive microcephaly.

This means that the overall chance of a second child being born is between 10% and 20%. However, if the parents go on to have a second affected child, the chance usually rises to 25% for a third affected child, assuming an autosomal recessive inheritance mechanism is accepted.

### **Prenatal Ultrasound Diagnosis of Microcephaly**

This is a difficult area. For some families this option is not available because careful examination of the affected child's OFC growth chart indicates that microcephaly only became apparent in the first few months after birth.

Even in instances where the affected child was born with microcephaly (congenital microcephaly), it is possible that prenatal ultrasound measurements would not have shown slowing of the head growth until very late in the pregnancy.

For a few families only, ultrasound has been used to diagnose severe, genetic microcephaly early enough in pregnancy to permit the option of termination at the parents' request.

The above account provides only a basic summary of information about genetic microcephaly. Many more details may be found in Internet publications both technical medical accounts and also in the information posted by families who have done their own research. Sometimes, the information that is supplied is confusing and one role of the clinical geneticist is to guide and provide clearer explanations for families who wish to learn more about microcephaly. include MCPH2, MCPH3, and MCPH4. In the future, in this group of conditions, tests may become available that permit diagnosis of microcephaly in early pregnancy. Each region in the UK has a designated clinical genetics centre that may be contacted by doctors and families who may wish to seek details of genetic or hereditary conditions. Locations and contact details for each clinical genetics centre are available at <http://www.bshg.org.uk/>