What causes MPPH syndrome?

Mutations (changes) in the *AKT3*, *PIK3R2* or *CCND2* genes can cause MPPH syndrome. These mutations result in an increase in the overall number of nerve cells in the developing brain, which results in a large brain and disruption of the very carefully organized cerebral grey matter (cortex). These changes lead to the developmental delay and seizures seen in the condition. It is not clear how these mutations result in the extra fingers or toes.

Why did this happen?

When children are conceived their parents' genetic material is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and occasionally random, rare changes occur in the genetic code of children that are not seen in the DNA of their parents. MPPH syndrome occurs when one of these random, rare changes affects one of three genes - *AKT3*, *PIK3R2* or *CCND2*. These types of change happen naturally in all species - humans, plants and animals - and are not due to your lifestyle or anything you did.

In most families the DNA change occurs out of the blue (de novo). There is one family in which a very mildly affected mother had a mutation in *CCND2* in a very small proportion of her cells, and went on to have a child with MPPH syndrome.

Can it happen again?

The risk of having another child affected by a rare gene disorder depends on the genetic code of the parents. For MPPH syndrome where parents do not carry the mutation, the chances of having another child are almost certainly no higher than for anyone else in the population. If the genetic analysis of the parents of a child with MPPH shows they carry the same variant, the chance of it happening again is much higher. Each family situation is different and a clinical geneticist can give you specific advice for your family.

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This guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. This guide was written by Dr Eamonn Sheridan, Senior Lecturer in Clinical Genetics, Leeds Institute for Molecular Medicine, UK.

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MPPH syndrome

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What is MPPH syndrome?

Megalencephaly-postaxial polydactyly-polymicrogyria -hydrocephalus (MPPH) syndrome was first described as a distinct syndrome in 2004; subsequently a total of 18 patients were reviewed in detail in 2011. The name describes the main features of the disorder.

Megalencephaly refers to overgrowth of the brain.

Postaxial polydactyly is the presence of extra fingers or toes on the outer side of the hands and/or feet.

Polymicrogyria is a disorder of the organisation of the grey matter of the brain.

Hydrocephalus is the abnormal accumulation of fluid in the ventricles of the brain, considered to be a consequence of the megalencephaly.

The condition arises as a result of mutations (changes) in a group of related genes: *AKT3, PIK3R2, or CCND2.*

AKT3 is a gene on chromosome 1 in the band known as 1q44 between base pairs 243651534 and 244014380.

PIK3R2 is a gene on chromosome 19 in the band known as 19p13.11 between base pairs 18263987 and 18281342.

CCND2 is a gene on chromosome 12 in the band known as 12p13.32 between base pairs 4382900 and 4414521.

Can this be cured?

MPPH syndrome cannot be cured at the present time. If hydrocephalus is present and causes increased pressure in the brain, this can be treated.

Development

- Growth

Physical development tends to be fairly normal. All children have a big head and some children do have some minor degree of general overgrowth.

- Learning

Developmental delay ranging from mild to severe is present in nearly everyone. Some children learn to talk and walk, but many have few words and walking is not possible for everyone.

- Behaviour

Autistic features have been recorded in some children and stereotypies (e.g. hand flapping) have been reported.

- Speech

Delay in the development of speech is very common and some children will not acquire speech, using other means to communicate. It is difficult to predict how well speech will develop.

- Appearance

Certain facial features are reported commonly. These include a prominent forehead, a low bridge to the nose, and apparently wide-spaced eyes (hypertelorism) . These are all likely to be a result of the large head

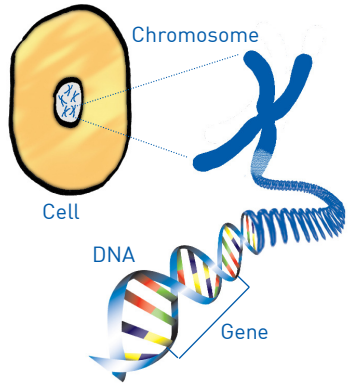
Management recommendations

The treatment of MPPH is essentially supportive and symptomatic. Seizures are treated with standard anti-epileptic medication; speech therapy and physiotherapy will help with learning to talk and walk. Caution should be exercised in the use of a shunting procedure to treat hydrocephalus. The primary disorder here is one of brain growth, which is unaffected by shunting.

Most people with MPPH syndrome have:

- Developmental delay, slow learning and intellectual disability
- Seizures (epilepsy)
- Abnormalities of muscle tone are common, particularly reduced muscle tone in infancy.
- Large head (megalencephaly)
- Characteristic appearance with a broad, prominent forehead
- Polymicrogyria (PMG), an abnormal organization of the grey matter (cortex). PMG can affect smaller or larger parts of the cortex, which is at the surface of the brain
- Extra fingers and/or toes are seen in a proportion of children with MPPH syndrome.

Medical concerns



Megalencephaly

A head size which is larger than expected for age is seen in everyone with the syndrome. Often the head is big at birth, and tends to go on growing at an increased rate.

Ventriculomegaly

The cerebral ventricles are normal spaces in the brain filled with cerebrospinal fluid (CSF). The ventricles are often expanded in children with MPPH syndrome; this is called ventriculomegaly. It is usually diagnosed on a brain scan, usually an MRI scan. Several children with the condition have had a surgical procedure to reduce the ventriculomegaly to try to control head growth. However, as the underlying cause of the head growth is a progressive overgrowth of the brain, the procedure is usually unsuccessful and unnecessary.

Polydactyly Extra fingers or toes (digits) are not seen in everyone with MPPH syndrome. They can affect one or both hands or feet. The extra digits can be removed if this will improve function or if people request it.

Polymicrogyria (PMG) Polymicrogyria is a necessary feature and can be best diagnosed by means of an MRI brain scan. Other unusual features that can be seen on an MRI scan in MPPH syndrome include abnormalities of the corpus callosum (connection between the two halves of the brain, the hemispheres), white matter abnormalities, and cerebellar tonsillar ectopia, where part of the under-surface of the cerebellum at the back and base of the brain is unusually low-lying.

Seizures Epilepsy is very common, but not found in all children with MPPH and different types can occur. Infantile spasms, generalized tonic clonic seizures, absence seizures, and partial seizures have all been recorded. There is a link between the severity of seizures and the degree of PMG.