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 anything a parent did or did not do.

In most families the change in any one of the three genes occurs out of the blue and is not inherited from one of the parents (*de novo* (dn)). In a small number of cases, one parent carries the change in some (but not all) of the cells in their body. This is called mosaicism. Parents with mosaicism may not have any symptoms but can still have a child with MPPH syndrome.

Can it happen again?

The chance of having another child affected by a rare gene disorder depends on the genetic code of the parents. If neither parent is found to carry a change in the *ATK3, PIK3R2* or *CCND2* genes, the chance of having another child with MPPH is very low. However, there is a small chance that some of the egg cells in the mother or some of the sperm cells in the father, carry the same change in one of these three genes (this is called germline (gonadal) mosaicism). This means that parents who are not found to carry the change when their blood is tested still have a very small chance of having another child with MPPH syndrome. If the genetic analysis of the parents of a child with MPPH syndrome 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 including, if applicable, options for testing regarding future pregnancies.

Can it be cured?

There is no cure for MPPH syndrome since the effects of the change took place during a baby's formation and development. However, knowing the diagnosis means that the appropriate monitoring and treatment can be put in place.

Management recommendations

Children with MPPH syndrome should be followed up by a general paediatrician who can oversee their care and monitor their development and symptoms.

Consultation with a specialist in the field of paediatric neurology, where seizures are suspected, and brain magnetic resonance imaging (MRI) to detect hydrocephalus and/or other brain anomalies is recommended. Seizures are treated with standard anti-epileptic medication. Close follow-up by a neurosurgeon for hydrocephalus, chiari malformations or other neurosurgical complications is recommended.

Assessment by a feeding specialist, nutritionist, and gastroenterologist for evidence of chewing and swallowing difficulties and dysphagia is advised. Regular screening for low blood sugar levels during the neonatal period, and review by an endocrinologist where hypoglycaemia is detected, is recommended. Echocardiogram (ECG) (to evaluate for cardiac (heart) anomalies) and renal ultrasound examination (to evaluate for structural anomalies of the kidneys, ureters and bladder) may be considered.

Speech therapy, occupational therapy and physiotherapy often prove beneficial.

Inform Network Support

Rare Chromosome Disorder Support Group

The Stables, Station Road West, Oxted, Surrey
RH8 9EE, UK
Tel/Fax: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support. Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at www.rarechromo.org/donate
Please help us to help you!

Facebook MPPH Syndrome
www.facebook.com/groups/459569770779913

 The original guide was written by Dr Eamonn Sheridan, Senior Lecturer in Clinical Genetics, Leeds Institute for Molecular Medicine, UK. The guide was updated by Joesph Butt (BSc MSc) and Unique (CA) in 2022 and reviewed by Dr Ghayda Mirzaa (MD), Associate Professor, Division of Genetic Medicine, Seattle, US.

2015 Version 1 (PM) 2022 Version 2 (JB/CA)

Rare Chromosome Disorder Support Group Charity Number 1110661
Registered in England and Wales Company Number 5460413

Understanding Chromosome & Gene Disorders

MPPH syndrome

rarechromo.org

What is MPPH syndrome and what causes it?

Megalencephaly-polydactyly-polymicrogyria-hydrocephalus (MPPH) syndrome was first described in 2004. To date, fewer than 100 individuals with MPPH syndrome have been described in the medical literature. The name of the syndrome describes the main features of the disorder:

Megalencephaly refers to overgrowth of the brain

Polydactyly is the presence of extra fingers or toes on the outer side of the hands and/or feet (postaxial)

Polymicrogyria is a condition that affects the organisation of the grey matter of the brain

Hydrocephalus is the build-up of excess fluid in the brain, considered to be a consequence of the megalencephaly.

Genes are instructions which have important roles in our growth and development. They are made up of DNA and are incorporated and organised into structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located inside our cells, the building blocks of our bodies.

MPPH syndrome occurs when one of the two copies of one of three genes does not function as expected. These genes are known as *PIK3R2*, *AKT3* and *CCND2*. MPPH syndrome can be caused by specific changes (known as pathogenic variants) in the sequence of one copy of any one of these three genes.

The genes associated with MPPH syndrome are located in different chromosomes:

AKT3: located in chromosome 1 in the region 1q43-q44

PIK3R2 : located in chromosome 19 in the region 19p13.11

CCND2: located in chromosome 12 in the region 12p13.32

When a change disrupts the function of one of these genes, this leads to overgrowth of the brain. Since each of these genes have similar roles in the development and maturation of the brain, changes in any one of the genes can have similar effects, although there is significant variation in the features observed among those with MPPH. It is becoming clear that some of this variation depends on which of the three genes is affected/disrupted.

Most children with MPPH syndrome have:

- Some degree of developmental delay, slow learning, and learning (intellectual) disability
- Low muscle tone (hypotonia)
- An enlarged brain (megalencephaly)
- Enlarged ventricles (ventriculomegaly) or hydrocephalus (sometimes requiring shunting)
- Characteristic facial features including a large head and a broad, prominent forehead
- The presence of extra fingers and/or toes (polydactyly)
- Difficulty controlling the muscles of the mouth (oromotor dysfunction)
- Seizures (epilepsy)
- Polymicrogyria (PMG)

Development and behaviour

- **Growth and feeding** In children with MPPH syndrome, physical development tends to progress as expected although all children have a big head and some children have some minor degree of general overgrowth. Some children have low muscle tone (hypotonia), particularly during infancy. Feeding can be challenging for some since MPPH syndrome can affect the ability to move the mouth (oromotor dysfunction). This can contribute to difficulty swallowing (dysphagia) and drooling. Some infants also have gastro-oesophageal reflux (GERD/GORD) (in which feeds readily return up the food passage), which may require treatment.
- **Sitting, moving and walking** All children with MPPH syndrome show a delay in reaching developmental milestones such as sitting and walking. This delay can range from mild to severe. Some children learn to walk independently, but this is not possible for all.
- **Learning** All children with MPPH syndrome have learning (intellectual) disability ranging from mild to severe.
- **Behaviour** Autistic features have been recorded in some children and stereotypies (repetitive behaviours such as hand flapping) have been reported.
- **Speech** Most children with MPPH syndrome have speech delay and some children may remain non-verbal. Children may have difficulty co-ordinating the movements of the mouth necessary for speech. Augmentative and Alternative Communication (ACC) methods, including pointing, gestures and high-tech communication systems (aided communication) may help non-verbal children communicate.
- **Appearance** Most children have facial features in common that are likely a result of an increased brain and head size. These include a prominent forehead, a low bridge to the nose and wide-spaced eyes (hypertelorism). Some children may also have extra fingers/toes (polydactyly).

Medical concerns

The clinical (medical) concerns observed in children with MPPH syndrome is extremely variable. Some children may have multiple medical concerns, which could include features that are not listed here.

Megalencephaly An increase in the size of the brain (megalencephaly) is seen in all children with MPPH syndrome. This leads to a head size that is larger than expected for age (macrocephaly). The size of the head may be large at birth or may become enlarged in infancy and tends to go on growing at an increased rate.

Ventriculomegaly Due to the large head size in MPPH, excess cerebrospinal fluid in the brain can occur and cause enlarged ventricles (ventriculomegaly) or hydrocephalus. These conditions can in turn result in developmental delay, hypotonia and seizures that are associated with MPPH syndrome. Untreated hydrocephalus may cause increased intra-cranial pressure.

The cerebral ventricles are normal spaces in the brain that are filled with cerebrospinal fluid. In ventriculomegaly, these ventricles are expanded. Most children with MPPH syndrome have some degree of venticulomegaly, which is usually diagnosed on a brain (MRI) scan. Almost half of these children have hydrocephalus, where enlargement of the ventricles is accompanied by an increase in the pressure in the brain. This needs to be carefully monitored and treated if necessary.

Polymicrogyria Polymicrogyria is a change in the formation of tissue in the brain known as grey matter and can be best diagnosed by MRI scan. It is characterised by the presence of more folds in the grey matter than normal. These folds are also smaller than would be expected. There is a large variation in the symptoms associated with polymicrogyria, which include seizures, global developmental delay, oromotor dysfunction and delayed intellectual development.

Other Brain Anomalies Other features that can be seen on an MRI scan in MPPH syndrome include changes in the development of the corpus callosum (connection between the two halves of the brain), changes to the formation of white matter (another type of brain tissue), and cerebellar tonsillar ectopia, where a part of a structure at the back and base of the brain (cerebellum) is low-lying.

Seizures Epilepsy of different types is estimated to occur in 50 % (1 in 2) children with MPPH syndrome. Infantile spasms, generalized tonic clonic seizures, absence seizures and partial seizures have all been reported. There is a link between the severity of seizures and the degree of polymicrogyria. Early on-set epilepsy and generalized epilepsy have been linked to more pronounced developmental delay and intellectual disability.

Medulloblastoma A few children with MPPH syndrome (specifically with genetic changes in CCND2) have developed medulloblastoma (a type of brain cancer). Therefore, brain MRI studies should be carefully evaluated.

Polydactyly Extra fingers or toes (digits) are seen in around half of children with MPPH syndrome and can be present on one or both hands or feet. The extra digits can be removed through surgery in cases where removal improves function or if it is requested.

Other features Other features have been reported in some individuals, including concerns with vision, such as cortical visual impairment (CVI) and blindness; low blood sugar levels (hypoglycaemia); heart issues (arrhythmia or structural issues); anomalies of the kidneys; and thyroid problems.