

Megalencephaly-Polymicrogyria-Polydactyly-Hydrocephalus Syndrome

Subjects: **Genetics & Heredity**

Contributor: Rita Xu

Megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) syndrome is a rare disorder that primarily affects the development of the brain.

genetic conditions

1. Introduction

Affected individuals are born with an unusually large brain and head size (megalencephaly). The head and brain continue to grow rapidly during the first 2 years of life. MPPH syndrome is also associated with a brain abnormality called bilateral perisylvian polymicrogyria (BPP). The surface of the brain normally has many ridges or folds, called gyri. In people with BPP, an area of the brain called the perisylvian region develops too many gyri, and the folds are irregular and unusually small. Other brain abnormalities, including a buildup of fluid in the brain (hydrocephalus), have also been reported in people with MPPH syndrome.

The problems with brain development cause a variety of neurological signs and symptoms. People with MPPH syndrome have delayed development and intellectual disability that ranges from mild to severe. About half of affected individuals develop recurrent seizures (epilepsy) beginning early in childhood. People with MPPH syndrome also have difficulty coordinating movements of the mouth and tongue (known as oromotor dysfunction), which leads to drooling, difficulty swallowing (dysphagia), and a delay in the production of speech (expressive language).

About half of people with MPPH syndrome have an extra finger or toe on one or more of their hands or feet (polydactyly). The polydactyly is described as postaxial because it occurs on the same side of the hand or foot as the pinky finger or little toe.

The brain abnormalities characteristic of MPPH syndrome are also found in a closely related condition called megalencephaly-capillary malformation syndrome (MCAP). However, MCAP includes abnormalities of small blood vessels in the skin (capillary malformations) and several other features that are not usually part of MPPH syndrome.

2. Frequency

MPPH syndrome appears to be a rare disease. About 60 affected individuals have been described in the medical literature.

3. Causes

MPPH syndrome can be caused by mutations in the *AKT3*, *CCND2*, or *PIK3R2* gene. The proteins produced from all three genes are involved in a chemical signaling pathway called the PI3K-AKT-mTOR pathway. This signaling influences many critical cell functions, including the creation (synthesis) of new proteins, cell growth and division (proliferation), and the survival of cells. The PI3K-AKT-mTOR pathway is essential for the normal development of many parts of the body, including the brain.

Mutations in the *AKT3*, *CCND2*, or *PIK3R2* gene increase the activity of their respective proteins or prevent the proteins from being broken down when they should. As a result, chemical signaling through the PI3K-AKT-mTOR pathway is enhanced, which increases cell growth and division. In the brain, the increased number of cells leads to rapid and abnormal brain growth starting before birth. The rapid growth disrupts the structure and function of the developing brain. It is less clear how increased PI3K-AKT-mTOR signaling contributes to polydactyly, although the extra digits are probably related to abnormal cell proliferation in the developing hands and feet. *CCND2* and *PIK3R2* gene mutations are more likely to cause polydactyly than are *AKT3* gene mutations.

3.1. The Genes Associated with Megalencephaly-Polymicrogyria-Polydactyly-Hydrocephalus Syndrome

- *AKT3*
- *CCND2*
- *PIK3R2*

4. Inheritance

This condition is considered autosomal dominant, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Almost all cases of this condition result from new (*de novo*) gene mutations that occur during the formation of reproductive cells (eggs or sperm) or in early embryonic development. These cases occur in people with no history of the disorder in their family.

In a small number of cases, people with MPPH syndrome have inherited the altered gene from an unaffected parent who has a mutation only in their sperm or egg cells. This phenomenon is called germline mosaicism.

Rarely, the condition can also result from somatic mosaicism, in which some of an affected person's cells have a gene mutation and others do not. The genetic changes, which are called somatic mutations, arise randomly in one

cell during embryonic development. As cells continue to divide, only cells arising from the first abnormal cell will have the mutation.

5. Other Names for This Condition

- MEG-PMG-POLY-HYD
- megalencephaly-postaxial polydactyly-polymicrogyria-hydrocephalus syndrome
- MPPH
- MPPH syndrome

References

1. Mirzaa G, Dodge NN, Glass I, Day C, Gripp K, Nicholson L, Straub V, Voit T, Dobyns WB. Megalencephaly and perisylvian polymicrogyria with postaxialpolydactyly and hydrocephalus: a rare brain malformation syndrome associated withmental retardation and seizures. *Neuropediatrics*. 2004 Dec;35(6):353-9.
2. Mirzaa G, Parry DA, Fry AE, Giamanco KA, Schwartzenruber J, Vanstone M, LoganCV, Roberts N, Johnson CA, Singh S, Kholmansikh SS, Adams C, Hodge RD, HevnerRF, Bonthon DT, Braun KPJ, Faivre L, Rivière JB, St-Onge J, Gripp KW, ManciniGM, Pang K, Sweeney E, van Esch H, Verbeek N, Wieczorek D, Steinraths M, MajewskiJ; FORGE Canada Consortium, Boycot KM, Pilz DT, Ross ME, Dobyns WB, Sheridan EG. De novo CCND2 mutations leading to stabilization of cyclin D2 cause megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome. *Nat Genet*. 2014 May;46(5):510-515. doi: 10.1038/ng.2948.
3. Mirzaa GM, Conway RL, Gripp KW, Lerman-Sagie T, Siegel DH, deVries LS, Lev D, Kramer N, Hopkins E, Graham JM Jr, Dobyns WB. Megalencephaly-capillary malformation (MCAP) and megalencephaly-polydactyly-polymicrogyria-hydrocephalus(MPPH) syndromes: two closely related disorders of brain overgrowth and abnormal brain and body morphogenesis. *Am J Med Genet A*. 2012 Feb;158A(2):269-91. doi:10.1002/ajmg.a.34402.
4. Mirzaa GM, Rivière JB, Dobyns WB. Megalencephaly syndromes and activating mutations in the PI3K-AKT pathway: MPPH and MCAP. *Am J Med Genet C Semin MedGenet*. 2013 May;163C(2):122-30. doi: 10.1002/ajmg.c.31361.
5. Rivière JB, Mirzaa GM, O'Roak BJ, Beddaoui M, Alcantara D, Conway RL, St-Onge J, Schwartzenruber JA, Gripp KW, Nikkel SM, Worthylake T, Sullivan CT, Ward TR, Butler HE, Kramer NA, Albrecht B, Armour CM, Armstrong L, Caluseriu O, CytrynbaumC, Drolet BA, Innes AM, Lauzon JL, Lin AE, Mancini GM, Meschino WS, Reggin JD, Saggar AK, Lerman-Sagie T, Uyanik G, Weksberg R, Zirn B, Beaulieu CL; Finding of Rare Disease Genes (FORGE) Canada Consortium, Majewski J, Bulman DE, O'DriscollM, Shendure J, Graham JM Jr, Boycott KM,

Dobyns WB. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. *Nat Genet*. 2012 Jun 24;44(8):934-40.
doi:10.1038/ng.2331.

Retrieved from <https://encyclopedia.pub/entry/history/show/13724>