Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome

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

Frequency

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

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.

Inheritance Pattern

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.

Other Names for This Condition

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

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?/primer/testing/genetictesting
- Genetic Testing Registry: Megalencephaly-polymicrogyria-polydactyly-
• Genetic Testing Registry: Megalencephaly-polymicrogyria-polymyctaly-hydrocephalus syndrome 2

• Genetic Testing Registry: Megalencephaly-polymicrogyria-polymyctaly-hydrocephalus syndrome 3

Other Diagnosis and Management Resources
• GeneReview: MPPH Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK396098

Additional Information & Resources
Health Information from MedlinePlus
• Encyclopedia: Hydrocephalus
  https://medlineplus.gov/ency/article/001571.htm

• Encyclopedia: Increased Head Circumference
  https://medlineplus.gov/ency/article/003305.htm

• Encyclopedia: Intellectual Disability
  https://medlineplus.gov/ency/article/001523.htm

• Encyclopedia: Polydactyly
  https://medlineplus.gov/ency/article/003176.htm

• Health Topic: Brain Malformations
  https://medlineplus.gov/brainmalformations.html

• Health Topic: Hydrocephalus
  https://medlineplus.gov/hydrocephalus.html

Genetic and Rare Diseases Information Center
• Megalencephaly-Polymicrogyria-Polydactyly-Hydrocephalus syndrome

Additional NIH Resources
• National Institute of Neurological Disorders and Stroke: Hydrocephalus Fact Sheet
  https://www.ninds.nih.gov/Disorders/All-Diseases/Hydrocephalus-Information-Page

• National Institute of Neurological Disorders and Stroke: Megalencephaly Information Page
  https://www.ninds.nih.gov/Disorders/All-Diseases/Megalencephaly-Information-Page
Educational Resources

- MalaCards: megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 1
  https://www.malacards.org/card/megalencephaly_polymicrogyria_polydactyl_y_hydrocephalus_syndrome_1

- MalaCards: megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 2
  https://www.malacards.org/card/megalencephaly_polymicrogyria_polydactyl_y_hydrocephalus_syndrome_2

- MalaCards: megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 3
  https://www.malacards.org/card/megalencephaly_polymicrogyria_polydactyl_y_hydrocephalus_syndrome_3

- Orphanet: Megalencephaly-polymicrogyria-postaxial polydactyly-hydrocephalus syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=83473

- Unique: Rare Chromosome Disorder Support Group (UK)

Patient Support and Advocacy Resources

- American Epilepsy Society
  https://www.aesnet.org/

- Citizens United for Research in Epilepsy (CURE)
  https://www.cureepilepsy.org/

- Hydrocephalus Association
  https://www.hydroassoc.org/

- PMG Awareness Organization
  https://pmgawareness.org/

- The Arc: For People with Intellectual and Developmental Disabilities
  https://www.thearc.org/

Clinical Information from GeneReviews

- MPPH Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK396098
Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28megalencephaly-polymicrogyria-polydactyly-hydrocephalus+syndrome%5BTIAB%5D%29+OR+%28%28MPPH%5BTIAB%5D%29+AND+%28megalencephaly%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D

Catalog of Genes and Diseases from OMIM

- MEGALENCEPHALY-POLYMICROGYRIA-POLYDACTYLY-HYDROCEPHALUS SYNDROME 1
  http://omim.org/entry/603387

- MEGALENCEPHALY-POLYMICROGYRIA-POLYDACTYLY-HYDROCEPHALUS SYNDROME 2
  http://omim.org/entry/615937

- MEGALENCEPHALY-POLYMICROGYRIA-POLYDACTYLY-HYDROCEPHALUS SYNDROME 3
  http://omim.org/entry/615938

Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15627943

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22228622

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24705253
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4004933/
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23592320
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22729224
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3408813/

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