

MPPH Syndrome

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PIK3R2 gene

phosphoinositide-3-kinase regulatory subunit 2

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Normal Function

The PIK3R2 gene provides instructions for making one piece (subunit) of an enzyme called phosphatidylinositol 3-kinase (PI3K). The primary function of the subunit, which is known as P85, is to regulate the PI3K enzyme's activity. PI3K is a kinase, which means that it adds a cluster of oxygen and phosphorus atoms (a phosphate group) to other proteins through a process called phosphorylation. PI3K phosphorylates certain signaling molecules, which triggers a series of additional reactions as part of 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.

Health Conditions Related to Genetic Changes

Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome

At least four mutations in the PIK3R2 gene have been found to cause megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) syndrome. This rare condition affects the development of the brain, causing an unusually large brain and head size (megalencephaly) and other abnormalities of the brain's structure. Some affected individuals also have an extra finger or toe on one or more of their hands or feet (polydactyly). Each of the known mutations changes a single protein building block (amino acid) in the P85 subunit of PI3K. The most common mutation replaces the amino acid glycine with the amino acid arginine at position 373 (written as Gly373Arg or G373R). All of the mutations are described as "gain-of-function" because they increase the activity of PI3K. This enhanced activity increases chemical signaling through the PI3K-AKT-mTOR pathway, which leads to excessive cell growth and division. In the brain, the increased number of cells leads to rapid and abnormal brain growth starting before birth. It is less clear how these changes contribute to polydactyly, although the extra digits are probably related to abnormal cell proliferation in the developing hands and feet.

More About This Health Condition

Other disorders

Mutations in the PIK3R2 gene have been found to cause 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 unusually small. BPP is one of the major brain abnormalities associated with

MPPH syndrome (described above), but mutations in the PIK3R2 gene have also been identified in people with BPP who do not have the other signs and symptoms of MPPH syndrome. Like the genetic changes that cause MPPH syndrome, the PIK3R2 gene mutations associated with BPP are gain-of-function, ultimately leading to increased cell growth and division in the developing brain. The increased number of cells causes abnormal development of the gyri starting before birth. Gly373Arg, the most common mutation identified in people with MPPH syndrome, can also cause BPP. In some cases of BPP, a PIK3R2 gene mutation is present from birth in essentially every cell of the body. In other cases, the mutation is somatic, meaning it occurs at some point during embryonic development. As cells continue to grow and divide, some of these cells will have the genetic change, and others will not (a situation known as mosaicism). It is unclear why mutations in the same gene, and sometimes the very same mutation, cause BPP in some people and MPPH in others. It is possible that the number and location of brain cells that have the mutation (in cases of mosaicism) help determine which abnormalities of brain growth will occur.

Other Names for This Gene

p85 p85-BETA P85B phosphatidylinositol 3-kinase 85 kDa regulatory subunit beta
phosphatidylinositol 3-kinase regulatory subunit beta phosphatidylinositol 3-kinase, regulatory
subunit, polypeptide 2 (p85 beta) phosphoinositide-3-kinase regulatory subunit beta
phosphoinositide-3-kinase, regulatory subunit 2 (beta) PI3-kinase subunit p85-beta PI3K regulatory
subunit beta ptdIns-3-kinase regulatory subunit p85-beta

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

Tests of PIK3R2

Scientific Articles on PubMed

PubMed

Catalog of Genes and Diseases from OMIM

PHOSPHATIDYLINOSITOL 3-KINASE, REGULATORY SUBUNIT 2; PIK3R2

Gene and Variant Databases

NCBI Gene

ClinVar

References

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Genomic LocationThe PIK3R2 gene is found on chromosome 19.

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