DEPDC5 gene

DEP domain containing 5, GATOR1 subcomplex subunit

Normal Function

The *DEPDC5* gene provides instructions for making a protein that is one piece of a group of proteins (complex) called GATOR1. This complex is found in cells throughout the body, where it regulates a signaling pathway called the mTOR pathway. The mTOR pathway is involved in cell growth and division (proliferation), the survival of cells, and the creation (synthesis) of new proteins. The role of the GATOR1 complex is to block this pathway by inhibiting (stopping) the activity of a complex called mTOR complex 1 (mTORC1) that is integral to the mTOR pathway.

In the brain, the mTOR pathway regulates many processes, including the growth and development of nerve cells and their ability to change and adapt over time (plasticity).

Health Conditions Related to Genetic Changes

Familial focal epilepsy with variable foci

More than 80 mutations in the *DEPDC5* gene have been found to cause familial focal epilepsy with variable foci (FFEVF), which is an uncommon form of recurrent seizures (epilepsy) that runs in families. Affected individuals experience focal seizures, which are seizures that do not cause a loss of consciousness. Most of the *DEPDC5* gene mutations lead to the production of an abnormally short protein that is quickly broken down. As a result, formation of normal GATOR1 complex is reduced, leading to overactivity of mTORC1 and excessive signaling of the mTOR pathway. It is not clear how an abnormally active mTOR pathway leads to the focal seizures of FFEVF. Research suggests that increased mTOR pathway signaling in the brain leads to changes in the connections between nerve cells (synapses) and increased activation (excitation) of nerve cells, which can cause seizures.

For unknown reasons, some people with FFEVF caused by a *DEPDC5* gene mutation never develop the condition, a situation known as reduced penetrance. It is estimated that 60 percent of individuals with *DEPDC5* gene mutations go on to develop FFEVF.

Other disorders

Mutations in the *DEPDC5* gene can cause other seizure disorders, known as familial

mesial temporal lobe epilepsy and infantile spasms. Similar to individuals with FFEVF (described above), people with familial mesial temporal lobe epilepsy have focal seizures. They may also have feelings of déjà vu, fear, or nausea during the seizure. Infantile spasms are seizures that usually appear before the age of 1 and involve recurrent muscle contractions.

As in FFEVF, most of the *DEPDC5* gene mutations that cause familial mesial temporal lobe epilepsy or infantile spasms lead to reduced GATOR1 complex formation and an abnormally active mTOR pathway. It is unclear why individuals with mutations in the same gene develop different seizure disorders.

Other Names for This Gene

- DEP.5
- FFEVF
- FFEVF1
- KIAA0645

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of DEPDC5 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=9681[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28DEPDC5%5BTIAB%5D%29+OR+%28DEP+domain+containing+5%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- DEP DOMAIN-CONTAINING PROTEIN 5; DEPDC5 (https://omim.org/entry/614191)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/9681)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=DEPDC5[gene])

References

- Baldassari S, Licchetta L, Tinuper P, Bisulli F, Pippucci T. GATOR1 complex:the common genetic actor in focal epilepsies. J Med Genet. 2016 Aug;53(8):503-10.doi: 10.1136/jmedgenet-2016-103883. Epub 2016 May 19. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/27208208)
- Baulac S, Ishida S, Marsan E, Miquel C, Biraben A, Nguyen DK, Nordli D,Cossette P, Nguyen S, Lambrecq V, Vlaicu M, Daniau M, Bielle F, Andermann E,Andermann F, Leguern E, Chassoux F, Picard F. Familial focal epilepsy with focalcortical dysplasia due to DEPDC5 mutations. Ann Neurol. 2015 Apr;77(4):675-83.doi: 10.1002/ana.24368. Epub 2015 Mar 13. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/25623524)
- Baulac S. Genetics advances in autosomal dominant focal epilepsies: focus onDEPDC5. Prog Brain Res. 2014;213:123-39. doi: 10.1016/B978-0-444-63326-2.00007-7. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/25194487)
- Baulac S. mTOR signaling pathway genes in focal epilepsies. Prog Brain Res.2016; 226:61-79. doi: 10.1016/bs.pbr.2016.04.013. Epub 2016 Jun 7. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/27323939)
- Dibbens LM, de Vries B, Donatello S, Heron SE, Hodgson BL, Chintawar S, Crompton DE, Hughes JN, Bellows ST, Klein KM, Callenbach PM, Corbett MA, GardnerAE, Kivity S, Iona X, Regan BM, Weller CM, Crimmins D, O'Brien TJ, Guerrero-LopezR, Mulley JC, Dubeau F, Licchetta L, Bisulli F, Cossette P, Thomas PQ, Gecz J,Serratosa J, Brouwer OF, Andermann F, Andermann E, van den Maagdenberg AM,Pandolfo M, Berkovic SF, Scheffer IE. Mutations in DEPDC5 cause familial focalepilepsy with variable foci. Nat Genet. 2013 May;45(5):546-51. doi:10.1038/ng.2599. Epub 2013 Mar 31. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23542697)
- Ishida S, Picard F, Rudolf G, Noe E, Achaz G, Thomas P, Genton P, MundwillerE, Wolff M, Marescaux C, Miles R, Baulac M, Hirsch E, Leguern E, Baulac S.Mutations of DEPDC5 cause autosomal dominant focal epilepsies. Nat Genet. 2013May;45(5):552-5. doi: 10.1038/ng.2601. Epub 2013 Mar 31. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/23542701) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5010101/)
- Scheffer IE, Heron SE, Regan BM, Mandelstam S, Crompton DE, Hodgson BL, Licchetta L, Provini F, Bisulli F, Vadlamudi L, Gecz J, Connelly A, Tinuper P,Ricos MG, Berkovic SF, Dibbens LM. Mutations in mammalian target of rapamycinregulator DEPDC5 cause focal epilepsy with brain malformations. Ann Neurol. 2014May;75(5):782-7. doi: 10.1002/ana.24126. Epub 2014 Apr 14. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/24585383)
- van Kranenburg M, Hoogeveen-Westerveld M, Nellist M. Preliminary functionalassessment and classification of DEPDC5 variants associated with focal epilepsy.Hum Mutat. 2015 Feb;36(2):200-9. doi: 10.1002/humu.22723. Epub 2014 Nov 27. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/25366275)
- Weckhuysen S, Marsan E, Lambrecq V, Marchal C, Morin-Brureau M, An-Gourfinkell, Baulac M, Fohlen M, Kallay Zetchi C, Seeck M, de la Grange P,

Dermaut B, MeursA, Thomas P, Chassoux F, Leguern E, Picard F, Baulac S. Involvement of GATORcomplex genes in familial focal epilepsies and focal cortical dysplasia. Epilepsia. 2016 Jun;57(6):994-1003. doi: 10.1111/epi.13391. Epub 2016 May 13. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/27173016)

Genomic Location

The *DEPDC5* gene is found on chromosome 22 (https://medlineplus.gov/genetics/chromosome/22/).

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