ZIC2 gene

Zic family member 2

Normal Function

The *ZIC2* gene provides instructions for making a protein that plays an important role in the development of the front part of the brain (forebrain). This protein is a transcription factor, which means that it attaches (binds) to specific regions of DNA and helps control the activity of certain genes. The ZIC2 protein regulates genes involved in both early and late stages of forebrain development.

Health Conditions Related to Genetic Changes

Nonsyndromic holoprosencephaly

More than 80 mutations in the *ZIC2* gene have been found to cause nonsyndromic holoprosencephaly. This condition occurs when the brain fails to divide into two halves (hemispheres) during early development. *ZIC2* gene mutations are the second most common cause of nonsyndromic holoprosencephaly. The facial features of individuals with *ZIC2* gene mutations are different from those with nonsyndromic holoprosencephaly caused by mutations in other genes. These distinctive facial features include a narrowing of the head at the temples, outside corners of the eyes that point upward (upslanting palpebral fissures), large ears, a short nose with upturned nostrils, and a broad and deep space between the nose and mouth (philtrum). It is unclear how mutations in the *ZIC2* gene lead to these facial features.

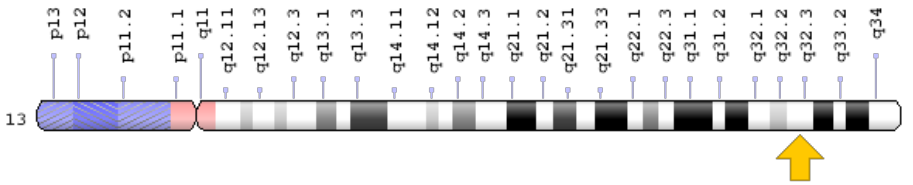
ZIC2 gene mutations that cause nonsyndromic holoprosencephaly reduce or eliminate the activity of the ZIC2 protein. Without enough functional ZIC2 protein, the genes involved in normal forebrain development are not properly controlled. As a result, the brain does not separate into two hemispheres. The signs and symptoms of nonsyndromic holoprosencephaly are caused by abnormal development of the brain and face.

Coloboma

Chromosomal Location

Cytogenetic Location: 13q32.3, which is the long (q) arm of chromosome 13 at position 32.3

Molecular Location: base pairs 99,981,784 to 99,986,765 on chromosome 13 (Homo sapiens Updated Annotation Release 109.20190607, GRCh38.p13) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- HPE5
- Zic family member 2 (odd-paired Drosophila homolog)
- Zic family member 2 (odd-paired homolog, Drosophila)
- ZIC2_HUMAN
- Zinc finger protein of the cerebellum 2
- zinc finger protein ZIC 2

Additional Information & Resources

Educational Resources

- Neuroscience (second edition, 2001): Formation of the Major Brain Subdivisions https://www.ncbi.nlm.nih.gov/books/NBK10954/

Clinical Information from GeneReviews

- Holoprosencephaly Overview https://www.ncbi.nlm.nih.gov/books/NBK1530

Scientific Articles on PubMed

- PubMed https://www.ncbi.nlm.nih.gov/pubmed?term=%28ZIC2%5BTIAB%5D%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

- ZIC FAMILY, MEMBER 2
  http://omim.org/entry/603073

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_ZIC2.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=ZIC2%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:12873
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:7546
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/7546
- UniProt
  https://www.uniprot.org/uniprot/O95409

Sources for This Summary

- Brown LY, Odent S, David V, Blayau M, Dubourg C, Apacik C, Delgado MA, Hall BD, Reynolds JF, Sommer A, Wieczorek D, Brown SA, Muenke M. Holoprosencephaly due to mutations in ZIC2: alanine tract expansion mutations may be caused by parental somatic recombination. Hum Mol Genet. 2001 Apr 1;10(8):791-6.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11285244
- Brown SA, Warburton D, Brown LY, Yu CY, Roeder ER, Stengel-Rutkowski S, Hennekam RC, Muenke M. Holoprosencephaly due to mutations in ZIC2, a homologue of Drosophila odd-paired. Nat Genet. 1998 Oct;20(2):180-3.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/9771712
- Dubourg C, Bendavid C, Pasquier L, Henry C, Odent S, David V. Holoprosencephaly. Orphanet J Rare Dis. 2007 Feb 2;2:8. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/17274816
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1802747/
- Roessler E, Lacbawan F, Dubourg C, Paulussen A, Herbergs J, Hehr U, Bendavid C, Zhou N, Ouspenskaia M, Bale S, Odent S, David V, Muenke M. The full spectrum of holoprosencephaly-associated mutations within the ZIC2 gene in humans predicts loss-of-function as the predominant disease mechanism. Hum Mutat. 2009 Apr;30(4):E541-54. doi: 10.1002/humu.20982.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19177455
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2674582/
- Roessler E, Muenke M. The molecular genetics of holoprosencephaly. Am J Med Genet C Semin Med Genet. 2010 Feb 15;154C(1):52-61. doi: 10.1002/ajmg.c.30236. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20104595
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2815021/

- Solomon BD, Gropman A, Muenke M. Holoprosencephaly Overview. 2000 Dec 27 [updated 2013 Aug 29]. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from http://www.ncbi.nlm.nih.gov/books/NBK1530/
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20301702
- Solomon BD, Lacbawan F, Mercier S, Clegg NJ, Delgado MR, Rosenbaum K, Dubourg C, David V, Olney AH, Wehner LE, Hehr U, Bale S, Paulussen A, Smeets HJ, Hardisty E, Tylki-Szymanska A, Pronicka E, Clemens M, McPherson E, Hennekam RC, Hahn J, Stashinko E, Levey E, Wieczorek D, Roeder E, Schell-Apacik CC, Booth CW, Thomas RL, Kenwrick S, Cummings DA, Bous SM, Keaton A, Balog JZ, Hadley D, Zhou N, Long R, Vélez JI, Pineda-Alvarez DE, Odent S, Roessler E, Muenke M. Mutations in ZIC2 in human holoprosencephaly: description of a novel ZIC2 specific phenotype and comprehensive analysis of 157 individuals. J Med Genet. 2010 Aug;47(8):513-24. doi: 10.1136/jmg.2009.073049. Epub 2009 Dec 2.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/19955556
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3208626/
- Solomon BD, Mercier S, Vélez JI, Pineda-Alvarez DE, Wyllie A, Zhou N, Dubourg C, David V, Odent S, Roessler E, Muenke M. Analysis of genotype-phenotype correlations in human holoprosencephaly. Am J Med Genet C Semin Med Genet. 2010 Feb 15;154C(1):133-41. doi: 10.1002/ajmg.c.30240. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20104608
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2815217/
- Warr N, Powles-Glover N, Chappell A, Robson J, Norris D, Arkell RM. Zic2-associated holoprosencephaly is caused by a transient defect in the organizer region during gastrulation. Hum Mol Genet. 2008 Oct 1;17(19):2986-96. doi: 10.1093/hmg/ddn197. Epub 2008 Jul 9.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18617531
- OMIM: ZIC FAMILY, MEMBER 2
  http://omim.org/entry/603073

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/ZIC2

Reviewed: September 2010
Published: September 10, 2019

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services