# Amish lethal microcephaly

## Description

Amish lethal microcephaly is a disorder in which infants are born with a very small head and underdeveloped brain.

Infants with Amish lethal microcephaly have a sloping forehead and an extremely small head size. They may also have an unusually small lower jaw and chin (micrognathia) and an enlarged liver (hepatomegaly).

Affected infants may have seizures and difficulty maintaining their body temperature. Often they become very irritable starting in the second or third month of life. A compound called alpha-ketoglutaric acid can be detected in their urine (alpha-ketoglutaric aciduria), and during episodes of viral illness they tend to develop elevated levels of acid in the blood and tissues (metabolic acidosis). Infants with this disorder typically feed adequately but do not develop skills such as purposeful movement or the ability to track faces and sounds. Affected infants live only about six months.

## Frequency

Amish lethal microcephaly occurs in approximately 1 in 500 newborns in the Old Order Amish population of Pennsylvania. It has not been found outside this population.

## Causes

Mutations in the *SLC25A19* gene cause Amish lethal microcephaly.

The *SLC25A19* gene provides instructions for producing a protein that is a member of the solute carrier (SLC) family of proteins. Proteins in the SLC family transport various compounds across the membranes surrounding the cell and its component parts. The protein produced from the *SLC25A19* gene transports a molecule called thiamine pyrophosphate into the mitochondria, the energy-producing centers of cells. This compound is involved in the activity of a group of mitochondrial enzymes called the dehydrogenase complexes, one of which is the alpha-ketoglutarate dehydrogenase complex. The transport of thiamine pyrophosphate into the mitochondria is believed to be important in brain development.

All known individuals with Amish lethal microcephaly have a mutation in which the protein building block (amino acid) alanine is substituted for the amino acid glycine at

position 177 of the SLC25A19 protein, written as Gly177Ala or G177A. Researchers believe that this mutation interferes with the transport of thiamine pyrophosphate into the mitochondria and the activity of the alpha-ketoglutarate dehydrogenase complex, resulting in the abnormal brain development and alpha-ketoglutaric aciduria seen in Amish lethal microcephaly.

Learn more about the gene associated with Amish lethal microcephaly

- SLC25A19

## Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

## Other Names for This Condition

- Amish microcephaly
- MCPHA
- Microcephaly, Amish type

## Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Amish lethal microcephaly (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1846648/)

Genetic and Rare Diseases Information Center

- Amish lethal microcephaly (https://rarediseases.info.nih.gov/diseases/8606/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Catalog of Genes and Diseases from OMIM

- MICROCEPHALY, AMISH TYPE; MCPHA (https://omim.org/entry/607196)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Microcephaly%5BMAJR%5D%29+AND+%28%28Amish%5BALL%5D%29+OR+%28mcpha%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

## References


- Kelley RI, Robinson D, Puffenberger EG, Strauss KA, Morton DH. Amish lethalmicrocephaly: a new metabolic disorder with severe congenital microcephaly and2-ketoglutaric aciduria. Am J Med Genet. 2002 Nov 1;112(4):318-26. doi:10.1002/ajmg.10529. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12376931)
- Korf BR. What's new in neurogenetics? Amish microcephaly. Eur J PaediatrNeurol. 2003;7(6):393-4. doi: 10.1016/j.ejpn.2003.09.005. No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/14623217)
- Lindhurst MJ, Fiermonte G, Song S, Struys E, De Leonardis F, Schwartzberg PL, Chen A, Castegna A, Verhoeven N, Mathews CK, Palmieri F, Biesecker LG. Knockoutof Slc25a19 causes mitochondrial thiamine pyrophosphate depletion, embryoniclethality, CNS malformations, and anemia. Proc Natl Acad Sci U S A. 2006 Oct24;103(43):15927-32. doi: 10.1073/pnas.0607661103. Epub 2006 Oct 11. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17035501) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1595310/)
- Rosenberg MJ, Agarwala R, Bouffard G, Davis J, Fiermonte G, Hilliard MS, KochT, Kalikin LM, Makalowska I, Morton DH, Petty EM, Weber JL, Palmieri F, KelleyRI, Schaffer AA, Biesecker LG. Mutant deoxynucleotide carrier is associated withcongenital microcephaly. Nat Genet. 2002 Sep;32(1):175-9. doi: 10.1038/ng948. Epub 2002 Aug 19. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/12185364)
- Siu VM, Ratko S, Prasad AN, Prasad C, Rupar CA. Amish microcephaly: Long-termsurvival and biochemical characterization. Am J Med Genet A. 2010Jul;152A(7):1747-51. doi: 10.1002/ajmg.a.33373. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20583149)
- Tabarki B, Thabet F, Alfadhel M. SLC25A19-Related Thiamine MetabolismDysfunction. 2003 Sep 4 [updated 2023 Mar 30]. In: Adam MP, Feldman J, Mirzaa GM,Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. GeneReviews(R) [Internet]. Seattle (WA): University of Washington,Seattle; 1993-2024. Available from http://www.ncbi.nlm.nih.gov/books/NBK1365/ Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20301539)


**Last updated July 1, 2013**