

Amish Lethal Microcephaly

Subjects: Genetics & Heredity

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

Keywords: genetic conditions

1. Introduction

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.

2. 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.

3. 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.

3.1. The gene associated with Amish lethal microcephaly

- *SLC25A19*

4. 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.

5. Other Names for This Condition

- Amish microcephaly
- MCPHA
- microcephaly, Amish type

References

1. Biesecker LG. Amish Lethal Microcephaly. 2003 Sep 4 [updated 2017 Dec 7]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from <http://www.ncbi.nlm.nih.gov/books/NBK1365/>
2. Kelley RI, Robinson D, Puffenberger EG, Strauss KA, Morton DH. Amish lethal microcephaly: a new metabolic disorder with severe congenital microcephaly and 2-ketoglutaric aciduria. *Am J Med Genet.* 2002 Nov 1;112(4):318-26.
3. Korf BR. What's new in neurogenetics? Amish microcephaly. *Eur J Paediatr Neurol.* 2003;7(6):393-4.
4. 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. Knockout of Slc25a19 causes mitochondrial thiamine pyrophosphate depletion, embryonic lethality, CNS malformations, and anemia. *Proc Natl Acad Sci U S A.* 2006 Oct 24;103(43):15927-32.
5. Rosenberg MJ, Agarwala R, Bouffard G, Davis J, Fiermonte G, Hilliard MS, Koch T, Kalikin LM, Makalowska I, Morton DH, Petty EM, Weber JL, Palmieri F, Kelley RI, Schäffer AA, Biesecker LG. Mutant deoxynucleotide carrier is associated with congenital microcephaly. *Nat Genet.* 2002 Sep;32(1):175-9.
6. Siu VM, Ratko S, Prasad AN, Prasad C, Rupar CA. Amish microcephaly: Long-term survival and biochemical characterization. *Am J Med Genet A.* 2010 Jul;152A(7):1747-51. doi: 10.1002/ajmg.a.33373.

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