GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Amish Lethal Microcephaly

[*Amish Microcephaly, MCPHA*]

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Initial Posting: September 4, 2003.
Last Update: December 20, 2005.

Summary

Disease characteristics. Amish lethal microcephaly is characterized by microcephaly and early death. The occipitofrontal circumference is typically six to 12 standard deviations below the mean; anterior and posterior fontanels are closed at birth and facial features are distorted. The average life span is between five and six months.

Diagnosis/testing. Amish lethal microcephaly is diagnosed by presence of microcephaly and a tenfold increase in the levels of the urinary organic acid 2-ketoglutarate. *SLC25A19* (also known as *DNC* or *MUP1*) is the only gene known to be associated with Amish lethal microcephaly. All affected individuals within the Old Order Amish population are homozygous for the same single-base pair substitution. Molecular genetic testing of the *SLC25A19* gene is available on a research basis only.

Management. Treatment for Amish lethal microcephaly is supportive only. Phenobarbital has been used to treat a few children with seizures. Physical therapy may alleviate contractures or other secondary neurologic manifestations. Childhood illnesses are managed to minimize acidosis.

Genetic counseling. Amish lethal microcephaly is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Prenatal molecular genetic testing may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

The sole major clinical finding is severe microcephaly present at birth [Kelley et al 2002]. Occipitofrontal circumference (OFC) is typically six to 12 standard deviations below the mean

Testing

Urinary organic acid 2-ketoglutarate. All affected children of Lancaster Amish heritage reported have highly elevated, at least tenfold-increasedf levels of the urinary organic acid 2-ketoglutarate, usually in the absence of increased levels of other citric acid cycle intermediates or lactate [Kelley et al 2002].

Note: No other metabolic abnormalities are consistently found. However, during intercurrent illnesses such as viral syndromes, some children have metabolic acidosis with increased concentration of lactate in blood and urine.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *SLC25A19* (also known as *DNC* or *MUP1*) is the only gene known to be associated with Amish lethal microcephaly.

Molecular genetic testing: Research

- **Sequence analysis.** All affected individuals within the Old Order Amish population are homozygous for the same single-base pair substitution, a 530G-C transversion in the *SLC25A19* gene [Rosenberg et al 2002].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Amish Lethal Microcephaly

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	530G-C transversion in SLC25A19	100% [1]	Research only

1. Note that the 100% mutation detection rate is for testing among the Amish; the yield would be expected to be lower in non-Amish individuals.

Genetically Related Disorders

No other phenotypes are known to be associated with mutations in *SLC25A19*.

Clinical Description

Natural History

Amish lethal microcephaly is a distinct disorder with little variability in its presentation, at least among the Old Order Amish from Lancaster County, Pennsylvania [Kelley et al 2002]. Affected infants have severe microcephaly at birth. The cranial vault is extremely underdeveloped as a result of the small brain size. Anterior and posterior fontanels are closed, and ridging from premature sutural fusion may be evident. The facial features are distorted due to the profound microcephaly. The only non-CNS physical anomaly is moderate micrognathia. Mild hepatomegaly has been observed in several affected individuals, usually during acute illnesses associated with metabolic acidosis.

Many affected infants have difficulty maintaining body temperature. After the first two or three months of life, increasing irritability of unknown causes commonly develops [Kelley et al 2002]. Although no changes in physical or neurologic examination accompany the irritability, children are more likely to die within 24-48 hours of developing their next viral illness. The average life span for an affected infant is between five and six months.

Neuropathology. A partial autopsy of an affected four-month-old infant gave insight into the neuropathology of the disorder [Strauss et al 2002]. The severity of the malformation is more pronounced in the anterior portion of the brain. Frontal lobes are smooth and rudimentary. Increasing convolution and lamination progresses occipitotemporally. Regions that are most hypoplastic are most disorganized histologically.

Genotype-Phenotype Correlations

At the present time, no data on genotype-phenotype correlations exist, as only one mutation has been identified.

Prevalence

Amish lethal microcephaly has been found only in the Old Order Amish who have ancestors in Lancaster County, Pennsylvania. At least 61 affected infants have been born to 33 nuclear families in the past 40 years. In this population, incidence is approximately one in 500 births.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Microcephaly has a wide variety of causative factors. It can be syndromic or isolated, environmental or genetic, congenital or acquired [Battaglia & Carey 2003]. A metabolic screen is indicated for all children with congenital microcephaly (urine organic acids, plasma amino acids, lactate, pyruvate, and electrolytes). Further specific evaluations are performed as indicated based on the results of this screen.

Microcephaly. The differential diagnosis for isolated congenital microcephaly includes single-gene disorders inherited in an autosomal recessive manner. Genes have been identified for four of six MCPH loci. The causative genes are as follows: *MCPH1* (encoding microcephalin) (MCPH1 locus); *CDK5RAP2* (MCPH3 locus), *ASPM* (MCPH5 locus), and *CENPJ* (MCPH6 locus). The genes at the MCPH2 locus and MCPH4 locus are still unknown. The degree of microcephaly is much greater in Amish lethal microcephaly than in any of these other genetically defined microcephaly syndromes. Additionally, 2-ketoglutaric aciduria has not been reported as a finding with these disorders. Other causative genes for isolated congenital microcephaly are unknown and unmapped.

Microcephaly may also be inherited in an autosomal dominant manner and possibly in an X-linked manner, though the causative genes have not been identified [Battaglia & Carey 2003].

Alpha-ketoglutarate. Elevated levels of alpha-ketoglutarate may also be seen in individuals with mutations in the alpha-ketoglutarate dehydrogenase complex, but this phenotype does not typically present with microcephaly [Kohlschutter et al 1982].

Increased levels of 2-ketoglutarate are common in a wide variety of disorders of mitochondrial function, including those caused by mutations of both mtDNA and nuclear DNA genes (see Mitochondrial Disorders Overview).

Among other genetic malformation syndromes, a similar level of 2-ketoglutarate is also characteristic of the autosomal recessive form of DOOR syndrome (**d**eafness, **o**nychodystrophy, **o**steodystrophy, and mental **r**etardation; OMIM 220500), for which the causative genetic defect has not yet been determined.

Management

Evaluation at Initial Diagnosis to Establish Extent of the Disease

Appropriate imaging studies should be performed; refer to general references on microcephaly for guidance as no recommendations are specific to MCPHA.

Treatment of Manifestations

- This disorder is uniformly fatal (typically within the first year of life). No intervention — including mitochondrial vitamin treatment — has shown promise for treatment or amelioration. However, the disorder has only been reported among the Old Order Amish; therefore, all clinical experience is based on a single allele. Other alleles may be less severe.
- Seizures have occurred in some affected infants; the few children who were treated responded well to phenobarbital.
- Physical therapy may be considered if the children develop contractures or other secondary neurologic manifestations.
- Early intervention may be considered to stimulate and comfort the infant.
- Support and respite for the family may be needed during the stressful terminal irritability phase of the disease, which can last for several weeks.

Prevention of Primary Manifestations

Routine childhood illnesses should be managed to minimize the acidosis associated with acute illnesses. Many affected infants have died during metabolic exacerbations associated with an intercurrent illness.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Vitamin supplementation does not appear to be effective.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Amish lethal microcephaly is inherited in an autosomal recessive manner.

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- The parents of an affected individual are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic and have normal urinary excretion of 2-ketoglutarate.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. Amish lethal microcephaly is lethal before reproductive age.

Other family members. The risk to each sib of the proband's parents of being a carrier is at least 50% and may be 67% (2/3) if the proband's parent had an affected sib.

Carrier Detection

Carrier testing using molecular genetic techniques is not offered because it is not clinically available.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of Amish lethal microcephaly are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research laboratory. For laboratories offering custom prenatal testing, see 

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Three fetal ultrasound examinations performed after 20 weeks' gestation in two pregnancies of babies ultimately found to have Amish lethal microcephaly revealed marked deceleration of head growth [Kelley et al 2002]. The sensitivity and specificity of fetal ultrasound for the

prenatal diagnosis of Amish lethal microcephaly has not been evaluated. Prenatal diagnosis by measurement of 2-ketoglutarate in amniotic fluid has also has not been evaluated.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Amish Lethal Microcephaly

Gene Symbol	Chromosomal Locus	Protein Name
SLC25A19	17q25.3	Mitochondrial deoxynucleotide carrier

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Amish Lethal Microcephaly

606521	SOLUTE CARRIER FAMILY 25 (MITOCHONDRIAL DEOXYNUCLEOTIDE CARRIER), MEMBER 19; SLC25A19
607196	MICROCEPHALY, AMISH TYPE; MCPHA

Table C. Genomic Databases for Amish Lethal Microcephaly

Gene Symbol	Entrez Gene	HGMD
SLC25A19	60386 (MIM No. 606521)	SLC25A19

For a description of the genomic databases listed, click here.

Normal allelic variants: *SLC25A19* contains nine exons that span 16.5 kb [Iacobazzi et al 2001]. Translation begins in exon 4 and there is evidence of alternate splicing of the three untranslated 5-prime exons.

Pathologic allelic variants: One known genetic alteration results in MCPHA [Rosenberg et al 2002]. A single-nucleotide substitution, c.530G↓C (Genbank NM_021734), which predicts p.G177A (OMIM #607196.0001), was found in homozygous form in affected individuals. This substitution was not found in 252 chromosomes from non-Amish individuals tested by a PCR-amplified restriction fragment length polymorphism assay. (For more information, see Genomic Databases table above.)

Normal gene product: The DNC protein contains three predicted mitochondrial carrier motifs characteristic of proteins, including the 2-ketoglutarate transporter, found in the inner mitochondrial membrane [Dolce et al 2001]. Functional analysis using bacterially expressed protein reconstituted in proteoliposomes revealed that DNC can catalyze the transport of deoxynucleotide diphosphates, deoxynucleotide triphosphates, and dideoxynucleotide triphosphates in exchange for dNDPs, ADP, or ATP. It is predicted that DNC catalzyes the uptake of dNDPs into the mitochondrial matrix.

Abnormal gene product: A bacterially expressed DNC protein containing the p.G177A substitution reconstituted in proteoliposomes was unable to catalyze the exchange of α-S^{35}dATP for ADP and is therefore predicted to be nonfunctional with respect to deoxynucleotide transport [Rosenberg et al 2002]. The relationship between the abnormal gene product and the diagnostically important 2-ketoglutaric aciduria is not understood.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

National Institute of Neurological Disorders and Stroke
Microcephaly Information Page

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

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Chapter Notes

Author Notes

Dr. Lindhurst is a geneticist and senior biologist trained at the University of Chicago. Dr. Biesecker is a clinical geneticist and human geneticist and trained at the University of Michigan. Both are based at the National Human Genome Research Institute at the NIH.

Revision History

- 20 December 2005 (me) Comprehensive update posted to live Web site
- 4 September 2003 (me) Review posted to live Web site
- 24 June 2003 (mjl) Original submission