GENEReviews

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

Mucolipidosis IV

Raphael Schiffmann, MD
Lead Investigator, Developmental and Metabolic Neurology Branch
National Institute of Neurological Disorders and Stroke
National Institutes of Health
schiffmr@ninds.nih.gov

Susan A Slaugenhaupt, PhD
Harvard Institute of Human Genetics
susan_slaugenhaupt@hms.harvard.edu

Janine Smith, MD
National Eye Institute
National Institutes of Health
jmas@box-j.nih.gov

Ehud Goldin, PhD
Section on Molecular Neurogenetics
Medical Genetics Branch
National Human Genome Research Institute
National Institutes of Health

Initial Posting: January 28, 2005.
Last Update: June 6, 2007.

Summary

Disease characteristics. Mucolipidosis IV is characterized by severe psychomotor delay evident by the end of the first year of life and slowly progressive visual impairment during the first decade as a result of a combination of corneal clouding and retinal degeneration. By the end of the first decade of life and certainly by their early teens, all individuals with typical mucolipidosis IV have severe visual impairment as a result of retinal degeneration. Neurodegeneration is observed in about 15% of individuals. About 5% of individuals have atypical mucolipidosis IV, often manifest as less severe psychomotor retardation and/or eye findings. About 70% of individuals with mucolipidosis IV are of Ashkenazi Jewish heritage.

Diagnosis/testing. Mucolipidosis IV is suspected in individuals with typical clinical findings and elevated plasma gastrin concentration or polymorphic lysosomal inclusions in skin or conjunctival biopsy. Molecular genetic testing of *MCOLN1*, the only gene known to be associated with mucolipidosis IV, confirms the diagnosis in most individuals. Two mutations, c.406-2A>G and g.511_6943del, account for 95% of mutations in individuals of Ashkenazi Jewish heritage. Such testing is clinically available. Sequencing of genomic DNA or cDNA detects mutations in the remaining 5% of individuals of Ashkenazi Jewish heritage and about 99% of individuals of non-Ashkenazi Jewish heritage. Such testing is available on a research basis only.

Management. *Treatment of manifestations:* speech therapy; physical therapy for spasticity and ataxia; ankle-foot orthotics (AFOs) as needed; anti-epileptic drugs (AED) as needed; topical lubricating eye drops, artificial tears, gels, or ointments for ocular irritation; surgical correction of strabismus; high-contrast black and white materials for those with visual impairment. *Prevention of secondary complications:* physical therapy to prevent permanent

joint contractures; oral iron to prevent iron deficiency anemia from poor absorption of dietary iron.

Genetic counseling. Mucolipidosis IV 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. Prenatal testing is available for at-risk pregnancies in families in which both disease-causing mutations have been identified.

Diagnosis

Clinical Diagnosis

Mucolipidosis IV should be suspected in any individual with the following:

- Early onset of developmental delay whether static, as in cerebral palsy, or progressively declining with loss of previously acquired cognitive and motor abilities [Altarescu et al 2002]
- Dystrophic retinopathy with or without corneal clouding [Smith et al 2002]

Testing

Plasma gastrin concentration is elevated in virtually all individuals with mucolipidosis IV (mean 1507 pg/mL; range 400-4100 pg/mL) (normal 0-200 pg/mL) [Schiffmann et al 1998, Altarescu et al 2002].

Biopsy of skin or conjunctiva shows accumulation of abnormal lamellar membrane structures and amorphous cytoplasmic inclusions in diverse cell types. Note: In the past, these findings were used to confirm the diagnosis of mucolipidosis IV [Prasad et al 1996, Bargal et al 2002]; more recently, however, demonstration of typical vacuolation by PAS staining of conjunctival cells obtained with a swab has been used for diagnosis [Smith et al 2002].

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. *MCOLN1* is the only gene associated with mucolipidosis IV.

Clinical testing

- **Targeted mutation analysis.** An estimated 70% of individuals with mucolipidosis IV are of Ashkenazi Jewish heritage [Altarescu et al 2002]. Two mutations, c.406-2A>G and g.511_6943del, account for 95% of mutations in individuals of Ashkenazi Jewish heritage.
  - Approximately 60% of individuals with mucolipidosis IV of Ashkenazi Jewish heritage in the US are homozygotes for the c.406-2A>G intronic acceptor splice-site mutation.
  - An estimated 33% are compound heterozygotes for the two common mutations [Wang et al 2001, Goldin et al 2004].

- Only one individual homozygous for the g.511_6943del mutation has been identified [Bargal et al 2000, Bassi et al 2000, Sun et al 2000].

Research testing

- **Sequence analysis.** Sequencing of genomic DNA or cDNA detects mutations in the remaining 5% of individuals of Ashkenazi Jewish heritage and about 99% of individuals of non-Ashkenazi Jewish heritage.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Mucolipidosis IV

Test Method	Mutations Detected	Mutation Detection Frequency [1]		Test Availability
		Ashkenazi Jewish	Non-Ashkenazi Jewish	
Targeted mutation analysis	c.406-2A>G, g.511_6943del	95%	6%-10%	Clinical Testing
Sequence analysis	*MCOLN1* sequence variants	5%	99%	Research only

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method

Testing Strategy

To establish the diagnosis in a proband

- Plasma gastrin concentration
- Molecular genetic testing: targeted mutation analysis in individuals of Ashkenazi heritage
- Skin biopsy or conjunctival swab if molecular genetic testing is not available

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in an affected family member.

Note: Carriers are heterozygous for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutations in an affected family member.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *MCOLN1*.

Clinical Description

Natural History

Mucolipidosis IV is a neurodevelopmental disorder that is also neurodegenerative in about 15% of individuals. The phenotype in affected individuals can be considered either typical (about 95% of individuals) or atypical (about 5% of individuals) [Altarescu et al 2002]. Although individuals with mucolipidosis IV typically survive to adulthood, it is believed that the life expectancy is reduced compared to healthy individuals.

Typical mucolipidosis IV. The most common presentation is severe psychomotor delay by the end of the first year of life in a child who is subsequently noted to have visual impairment caused by a combination of corneal clouding and retinal degeneration.

Psychomotor development is usually limited to few or no words and poor hand use [Altarescu et al 2002]; some may develop the ability to sit independently or crawl. Although most individuals do not achieve independent walking [Altarescu et al 2002], a few have learned to walk with the aid of a walker [Altarescu et al 2002].

Receptive language is better than expressive language; some individuals have used up to 50 signs to communicate.

Neurologic examination typically reveals severe dysarthria or anarthria, slow chewing, slow eating and swallowing, and spastic diplegia or quadriplegia [Altarescu et al 2002]. Individuals may be hypotonic, but tendon reflexes are usually hyperactive.

Neurologic deficits generally remain static during the first three decades of life [Altarescu et al 2002], although some individuals have neurologic deterioration.

MRI typically shows hypoplasia of the corpus callosum with absent rostrum and a dysplastic or absent splenium, signal abnormalities in the white matter on T1-weighted images, and increased ferritin deposition in the thalamus and basal ganglia. Atrophy of the cerebellum is observed in older individuals [Frei et al 1998].

Epileptiform discharges are common but are infrequently associated with clinical seizures [Siegel et al 1998].

Individuals with typical mucolipidosis IV have superficial corneal clouding that is bilateral, symmetric, and most visible in the central cornea [Smith et al 2002]. The corneal opacification is limited to the epithelium without stromal involvement or edema [Authors, personal observation], despite early reports of stromal abnormalities. On occasion, corneal clouding is the feature that prompts medical evaluation.

Painful episodes consistent with corneal erosions are common, but appear to decrease in frequency and severity with age.

Vision may be close to normal at a young age, but over the first decade of life, progressive retinal degeneration with varying degrees of vascular attenuation, retinal pigment epithelial changes, and optic nerve pallor result in further decrease in vision [Siegel et al 1998, Altarescu et al 2002, Pradhan et al 2002, Smith et al 2002]. Bilateral bull's eye maculopathy was observed in one individual [Smith et al 2002]. Visual acuity is difficult to test in most individuals with mucolipidosis IV, but is decreased in almost all persons over age five years. Virtually all individualsf with mucolipidosis IV develop severe visual impairment by their early teens as a result of the retinal degeneration.

Other ocular findings are strabismus (in more than half of individuals), nystagmus, ptosis, and cataract [Bach 2001, Smith et al 2002]. The pupillary response to light is usually sluggish without evidence of relative afferent pupillary defect [Smith et al 2002].

Iron deficiency occurs in about 50% and iron deficiency anemia, which is usually well tolerated, occurs in about 10% of individuals [Altarescu et al 2002].

The achlorhydria is asymptomatic.

The face is not typically coarse.

Affected individuals do not have hepatosplenomegaly or specific skeletal abnormalities.

Atypical and mild mucolipidosis IV. Individuals with atypical mucolipidosis IV are less severely affected than individuals with typical mucolipidosis IV or have one organ system disproportionately affected [Altarescu et al 2002].

Some individuals attain the ability to walk independently. They develop slowly progressive ataxia, have mild eye abnormalities, and are usually of non-Ashkenazi Jewish descent [Altarescu et al 2002].

Some present with a congenital myopathy with significant generalized hypotonia and elevated serum muscle creatine kinase concentration.

Some present with static (non-progressive) motor and cognitive delay and minimal ocular abnormalities.

- One female who presented with progressive visual impairment with corneal clouding with the appearance of cornea verticillata, retinopathy, normal psychomotor development, and behavioral abnormalities developed unstable gait in her twenties [Altarescu et al 2002].
- Two other individuals with no neurologic deficit were diagnosed based on ocular findings [Elleder, Schiffmann, & Goldin, unpublished]. The patient had all the other the typical features of mucolipidosis IV including achlorhydria and autofluorescent inclusions in cultured skin fibroblasts [Elleder, Schiffmann, & Goldin, unpublished].

Genotype-Phenotype Correlations

Ashkenazi Jewish individuals usually have the most severe form of the disease.

A splice mutation that causes a 15-bp deletion near the 3' end of *MCOLN1* (c.1406A>G, Table 3) discovered in a Canadian family from Newfoundland causes an atypical form of mucolipidosis IV, in which affected individuals walk independently and have better communicative skills [Altarescu et al 2002]. Missense mutations were found in the loop between the first and second transmembrane domain, one in the lipase domain, and one eliminating one of the four cysteines in the loop, possibly reducing the stability of mucolipin-1. Individuals with these mutations had a mild phenotype, an independent ataxic gait, and the ability to use their hands to feed themselves. The typical rather severe presentation associated with the c.694A>C mutation (p.Thr232Pro) in the same region may be explained by the fact that the mutated protein does not reach the endocytic compartment and accumulates in the endoplasmic reticulum [Manzoni et al 2004].

In several individuals from the southeast United States, a p.Asp362Tyr amino acid change was identified in the third transmembrane domain. This mutation was associated with a slower progression of the retinal disease and a relatively mild neurologic phenotype, although membrane preparations containing mucolipin-1 with this mutation had no channel activity [Raychowdhury et al 2004].

Several mutations were discovered in the fourth transmembrane domain, including the p.Phe408del that causes the mildest mucolipidosis IV phenotype known [Altarescu et al 2002]. The protein construct containing this mutation still functions as a channel in liposome preparations and only displays a deficiency in regulation [Raychowdhury et al 2004].

Several other mutations were discovered in the area of the presumed channel pore between the fifth and sixth transmembrane domain. Most of those were associated with a severe mucolipidosis IV phenotype (Table 3) [Altarescu et al 2002].

Nomenclature

Mucolipidosis IV was classified as a mucolipidosis because of the initial impression of simultaneous storage of lipids and water-soluble substances.

Prevalence

The combined carrier frequency of the two Ashkenazi Jewish mutations ranges from 1/100 to 1/127 in individuals of Ashkenazi Jewish descent [Bargal et al 2001, Edelmann et al 2002], although in a small group of 123 individuals, other investigators found a higher frequency [Wang et al 2001]. The splice mutation (c.406-2A>G) is at least three times more common than the deletion mutation (g.511_6943del) [Edelmann et al 2002]. The deletion mutation is particularly rare in the Israeli population (1/2000) in comparison to its frequency in the New York metropolitan area (1/406) [Bargal et al 2001, Edelmann et al 2002].

Prior to the availability of molecular diagnosis of mucolipidosis IV, individuals with atypical mucolipidosis IV were thought to have cerebral palsy, suggesting that mucolipidosis IV is underdiagnosed.

Differential Diagnosis

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

Because of the relatively static nature of the neurologic abnormality in mucolipidosis IV, individuals considered to have "cerebral palsy" should be evaluated for mucolipidosis IV.

The neurologic abnormalities and the finding of widespread storage material in tissue biopsy could suggest other lysosomal storage disorders such as mucolipidosis type I and type II and the mucopolysaccharidoses.

The finding of white matter abnormalities could suggest other inherited leukodystrophies such as Krabbe disease and metachromatic leukodystrophy.

Corneal clouding also occurs in the mucopolysaccharidoses (MPSI, MPSIII, MPSIV, MPSVI), mucolipidosis II and III, and GM1 gangliosidosis. Cornea verticillata (without retinal dystrophy) occurs in Fabry disease.

The retinal dystrophy of mucolipidosis IV is similar to that observed in the neuronal ceroid-lipofuscinoses and other genetic disorders with retinal degeneration such as Bardet-Biedl syndrome and Alström syndrome.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with mucolipidosis IV, the following evaluations are recommended:

- Ophthalmic examination
- Brain MRI
- Iron studies
- Neurologic evaluation, including EEG

Treatment of Manifestations

- Speech therapy
- Physical therapy and rehabilitation for motor dysfunction (mainly spasticity and ataxia)
- Ankle-foot orthotics in individuals with hypotonia and weakness of ankle dorsiflexion
- Anti-epileptic drugs (AED)
- Topical lubricating eye drops, artificial tears, gels, or ointments for management of the intermittent ocular irritation seen frequently in younger children
- Surgical correction of strabismus
- High-contrast black and white materials for those with visual impairment

Prevention of Secondary Complications

- Physical therapy and rehabilitation to prevent permanent joint contractures
- An oral iron preparation such as a ferrous sulfate to treat iron deficiency anemia resulting from poor absorption of dietary iron

Surveillance

Annual follow-up with a generalist is appropriate.

Testing of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Corneal transplantation has not been successful because the donor corneal epithelium is eventually replaced by the abnormal host epithelium.

Genetics clinics, staffed by genetics professionals, provide 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 may include disease-specific and/or umbrella support organizations.

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

Mucolipidosis IV is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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. Individuals with mucolipidosis IV do not reproduce. No information is available regarding the ability of individuals with mild disease to reproduce.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once both disease-causing mutations have been identified in an affected family member.

Population Screening

Because of the high carrier rate in individuals of Ashkenazi Jewish descent and the availability of premarital, preconception, and prenatal genetic counseling as well as prenatal diagnosis, mutation analysis of *MCOLN1* is often included in the panel of "Ashkenazi Jewish mutations" offered to individuals interested in preconception or prenatal risk assessment modification. Through this type of screening, couples in which both partners are carriers can be made aware of their status and risks before having affected children. Through genetic counseling and the option of prenatal testing, such families can, if they choose, bring to term only those pregnancies in which the fetus is unaffected.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing 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 the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at 25% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified or carrier status confirmed in both parents before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. 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 Mucolipidosis IV

Gene Symbol	Chromosomal Locus	Protein Name
MCOLN1	19p13.3-p13.2	Mucolipin-1

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 Mucolipidosis IV

252650	MUCOLIPIDOSIS IV
605248	MUCOLIPIN 1; MCOLN1

Table C. Genomic Databases for Mucolipidosis IV

Gene Symbol	Entrez Gene	HGMD
MCOLN1	57192 (MIM No. 605248)	MCOLN1

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

Molecular Genetic Pathogenesis

The lysosomal storage of lipids and water-soluble substances in mucolipidosis IV is attributed to a transport defect in the late steps of endocytosis resulting from abnormal membrane components of endosomes. Endosomes shuttle lipids and proteins between the plasma membrane and the various cellular organelles. Nutrients bound to lysosomes for processing would be retained in these transition vesicles. Alternatively it could indicate an increased rate of membrane recycling resulting from rapid degradation of malfunctioning protein complexes at the plasma membrane. Inability of cells to compensate for the missing cation channel function causes the defect in organization of white matter in the brain and reduces maintenance

of cells in the retina and optic nerve. Inability to secrete gastric acid may be directly related to a defect in the operation of the acid-secreting H^+K^+ ATPase in stomach parietal cells.

In *C. elegans* a mutation in an ABC transporter gene compensates for mucolipin deficiency and leads to viable worms, indicating that loss of a regulatory effect of mucolipin on the activity of the transporter is probably the cause of death in mucolipin-deficient worms [Schaheen et al 2006].

Normal allelic variants: *MCOLN1* spans 12,300 base pairs and contains 14 exons. In humans, no expressed splice variants are known. A single-nucleotide polymorphism, c.984C>T (p.Asn328Asn), results in no amino acid change (reference sequence NM_020553.1).

Pathologic allelic variants: A variety of mutations cause mucolipidosis IV, including splice mutations, small and large deletions and insertions, and point mutations that either cause stop codons or amino-acid changes in *MCOLN1* (Table 3). The two most prevalent mutations cause the majority of mucolipidosis IV in the Ashkenazi Jewish population. One is the splice mutation c.406-2A>G, which prevents splicing of mucolipin-1 mRNA at exon 4, resulting in a mix of unstable aberrant mRNA species. The second, g.511_6943del, is a deletion mutation that eliminates 6434 bp of DNA, including the first five exons and part of exon 6 of *MCOLN1*. A Polish individual with a non-Jewish haplotype was found to be heterozygous for this mutation [Sun et al 2000].

Missense mutations were found in the loop between the first and second transmembrane domain, one in the lipase domain and one eliminating the four cysteines in the loop, possibly reducing the stability of mucolipin. See Table 2 (pdf) for a summary of additional mutations not discussed in this review. For more information, see Genomic Databases table above.

Normal gene product: Mucolipin-1 is a 580-amino acid protein that is a member of the transient receptor potential (TRP) family. Proteins of this family are generally considered Ca^{2+} channels. Mucolipin-1 has a high homology to mucolipin-2 and mucolipin-3. It also shows homologies to polycystin-2, the product of *PKD2*, one of two genes associated with autosomal dominant polycystic kidney disease. Mucolipin-1 and polycystin-2 function as nonselective cation channels in heterologous expression systems [Fares & Greenwald 2001, LaPlante et al 2002, Slaugenhaupt 2002, Raychowdhury et al 2004, Treusch et al 2004].

Abnormal gene product: Most mutations are null alleles resulting in no gene product. When an abnormal gene product exists, it is a nonfunctional protein.

Table 3. *MCOLN1* Mutations Discussed in this *GeneReview*

Protein Change	DNA Change [1]	Reference Sequence [2]	Alias
	c.406-2A>G	NM_020533.1 AF287270	IVS3-2A↓G
	g.511_6943del	AF287270	
p.Thr232Pro	c.694A>C	NM_020533.1	
p.Asp362Tyr	c.1084G>T		
p.Phe408del	c.1221_1223delCTT		
p.Phe454_Asn569del	c.1406A>G		g.9107A>G

1. Mutations named according to HGVS nomenclature guidelines
2. Reference sequence at Genbank

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.

Mucolipidosis IV Foundation
719 East 17th Street
Brooklyn NY 11230
Phone: 718-434-5067
Email: www@ml4.org
www.ml4.org

National Mucopolysaccharidoses/Mucolipidoses Society (MPS), Inc
PO Box 736
Bangor ME 04402-0736
Phone: 207-947-1445
Fax: 207-990-3074
Email: info@mpssociety.org
www.mpssociety.org

Society for Mucopolysaccharide (MPS) Diseases
MPS House Repton Place White Lion Road
Amersham HP7 9LP
United Kingdom
Phone: 44 0845 389 9901
Email: mps@mpssociety.co.uk
www.mpssociety.co.uk

Chicago Center for Jewish Genetic Disorders
Ben Gurion Way
30 South Wells Street
Chicago IL 60606
Phone: 312-357-4718
Fax: 312-855-3295
Email: jewishgeneticsctr@juf.org
www.jewishgeneticscenter.org

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

Altarescu G, Sun M, Moore DF, Smith JA, Wiggs EA, Solomon BI, Patronas NJ, Frei KP, Gupta S, Kaneski CR, Quarrell OW, Slaugenhaupt SA, Goldin E, Schiffmann R. The neurogenetics of mucolipidosis type IV. Neurology. 2002;59:306–13. [PubMed: 12182165]

Bach G. Mucolipidosis type IV. Mol Genet Metab. 2001;73:197–203. [PubMed: 11461186]

Bargal R, Avidan N, Ben-Asher E, Olender Z, Zeigler M, Frumkin A, Raas-Rothschild A, Glusman G, Lancet D, Bach G. Identification of the gene causing mucolipidosis type IV. Nat Genet. 2000;26:118–23. [PubMed: 10973263]

Bargal R, Avidan N, Olender T, Ben Asher E, Zeigler M, Raas-Rothschild A, Frumkin A, Ben-Yoseph O, Friedlender Y, Lancet D, Bach G. Mucolipidosis type IV: novel MCOLN1 mutations in Jewish and non-Jewish patients and the frequency of the disease in the Ashkenazi Jewish population. Hum Mutat. 2001;17:397–402. [PubMed: 11317355]

Bargal R, Goebel HH, Latta E, Bach G. Mucolipidosis IV: novel mutation and diverse ultrastructural spectrum in the skin. Neuropediatrics. 2002;33:199–202. [PubMed: 12368990]

Bassi MT, Manzoni M, Monti E, Pizzo MT, Ballabio A, Borsani G. Cloning of the gene encoding a novel integral membrane protein, mucolipidin-and identification of the two major founder mutations causing mucolipidosis type IV. Am J Hum Genet. 2000;67:1110–20. [PubMed: 11013137]

Edelmann L, Dong J, Desnick RJ, Kornreich R. Carrier screening for mucolipidosis type IV in the American Ashkenazi Jewish population. Am J Hum Genet. 2002;70:1023–7. [PubMed: 11845410]

Fares H, Greenwald I. Regulation of endocytosis by CUP-5, the Caenorhabditis elegans mucolipin-1 homolog. Nat Genet. 2001;28:64–8. [PubMed: 11326278]

Frei KP, Patronas NJ, Crutchfield KE, Altarescu G, Schiffmann R. Mucolipidosis type IV: characteristic MRI findings. Neurology. 1998;51:565–9. [PubMed: 9710036]

Goldin E, Stahl S, Cooney AM, Kaneski CR, Gupta S, Brady RO, Ellis JR, Schiffmann R. Transfer of a mitochondrial DNA fragment to MCOLN1 causes an inherited case of mucolipidosis IV. Hum Mutat. 2004;24:460–5. [PubMed: 15523648]

LaPlante JM, Falardeau J, Sun M, Kanazirska M, Brown EM, Slaugenhaupt SA, Vassilev PM. Identification and characterization of the single channel function of human mucolipin-1 implicated in mucolipidosis type IV, a disorder affecting the lysosomal pathway. FEBS Lett. 2002;532:183–7. [PubMed: 12459486]

Manzoni M, Monti E, Bresciani R, Bozzato A, Barlati S, Bassi MT, Borsani G. Overexpression of wild-type and mutant mucolipin proteins in mammalian cells: effects on the late endocytic compartment organization. FEBS Lett. 2004;567:219–24. [PubMed: 15178326]

Pradhan SM, Atchaneeyasakul LO, Appukuttan B, Mixon RN, McFarland TJ, Billingslea AM, Wilson DJ, Stout JT, Weleber RG. Electronegative electroretinogram in mucolipidosis IV. Arch Ophthalmol. 2002;120:45–50. [PubMed: 11786056]

Prasad A, Kaye EM, Alroy J. Electron microscopic examination of skin biopsy as a cost-effective tool in the diagnosis of lysosomal storage diseases. J Child Neurol. 1996;11:301–8. [PubMed: 8807420]

Raychowdhury MK, Gonzalez-Perrett S, Montalbetti N, Timpanaro GA, Chasan B, Goldmann WH, Stahl S, Cooney A, Goldin E, Cantiello HF. Molecular pathophysiology of mucolipidosis type IV: pH dysregulation of the mucolipin-1 cation channel. Hum Mol Genet. 2004;13:617–27. [PubMed: 14749347]

Schaheen L, Dang H, Fares H. Basis of lethality in C. elegans lacking CUP-5, the Mucolipidosis Type IV orthologue. Dev Biol. 2006;293:382–91. [PubMed: 16530747]

Schiffmann R, Dwyer NK, Lubensky IA, Tsokos M, Sutliff VE, Latimer JS, Frei KP, Brady RO, Barton NW, Blanchette-Mackie EJ, Goldin E. Constitutive achlorhydria in mucolipidosis type IV. Proc Natl Acad Sci U S A. 1998;95:1207–12. [PubMed: 9448310]

Siegel H, Frei K, Greenfield J, Schiffmann R, Sato S. Electroencephalographic findings in patients with mucolipidosis type IV. Electroencephalogr Clin Neurophysiol. 1998;106:400–3. [PubMed: 9680151]

Slaugenhaupt SA. The molecular basis of mucolipidosis type IV. Curr Mol Med. 2002;2:445–50. [PubMed: 12125810]

Smith JA, Chan CC, Goldin E, Schiffmann R. Noninvasive diagnosis and ophthalmic features of mucolipidosis type IV. Ophthalmology. 2002;109:588–94. [PubMed: 11874766]

Sun M, Goldin E, Stahl S, Falardeau JL, Kennedy JC, Acierno JS Jr, Bove C, Kaneski CR, Nagle J, Bromley MC, Colman M, Schiffmann R, Slaugenhaupt SA. Mucolipidosis type IV is caused by

mutations in a gene encoding a novel transient receptor potential channel. Hum Mol Genet. 2000;9:2471–8. [PubMed: 11030752]

Treusch S, Knuth S, Slaugenhaupt SA, Goldin E, Grant BD, Fares H. Caenorhabditis elegans functional orthologue of human protein h-mucolipin-1 is required for lysosome biogenesis. Proc Natl Acad Sci U S A. 2004;101:4483–8. [PubMed: 15070744]

Wang ZH, Zeng B, Pastores GM, Raksadawan N, Ong E, Kolodny EH. Rapid detection of the two common mutations in Ashkenazi Jewish patients with mucolipidosis type IV. Genet Test. 2001;5:87–92. [PubMed: 11551108]

Suggested Readings

Bach G. Mucolipin 1: endocytosis and cation channel--a review. Pflugers Arch. 2005;451:313–7. [PubMed: 15570434]

Bach G, Webb MB, Bargal R, Zeigler M, Ekstein J. The frequency of mucolipidosis type IV in the Ashkenazi Jewish population and the identification of 3 novel MCOLN1 mutations. Hum Mutat. 2005;26:591. [PubMed: 16287144]

Chapter Notes

Revision History

- 6 June 2007 (me) Comprehensive update posted to live Web site
- 1 December 2005 (rs) Revision: sequence analysis no longer clinically available
- 28 January 2005 (me) Review posted to live Web site
- 16 August 2004 (rs) Original submission