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

Oculopharyngeal Muscular Dystrophy

[*OPMD*]

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Initial Posting: March 8, 2001.
Last Update: June 22, 2006.

Summary

Disease characteristics. Oculopharyngeal muscular dystrophy (OPMD) is characterized by late-onset (usually after the age of 45 years) eyelid drooping (ptosis, defined as either vertical separation of at least one palpebral fissure that measures less than 8 mm at rest), swallowing difficulty (dysphagia, defined as swallowing time greater than seven seconds when drinking 80 mL of ice-cold water), and a positive family history with involvement of two or more generations. In one study of autosomal dominant OPMD, the mean age of onset for ptosis was 48 years (range 26-65 years) and for dysphagia was 50 years (range 40-63 years). All individuals were symptomatic by age 70 years. Early symptoms of dysphagia are an increased time needed to complete a meal and an acquired avoidance of dry foods. Other signs observed as the disease progresses are tongue atrophy and weakness (82%), proximal lower extremity weakness (71%), dysphonia (67%), limitation of upward gaze (61%), facial muscle weakness (43%), and proximal upper extremity weakness (38%). Severe cases represent 5% to 10% of all cases. These individuals have earlier onset of ptosis and dysphagia (<45 years) and an incapacitating proximal leg weakness that starts before age 60 years. Some individuals eventually need a wheelchair. Life expectancy is not reduced.

Diagnosis/testing. Diagnosis of OPMD is based on clinical criteria. PABPN1, encoding the polyadenylate binding protein nuclear 1, is the only gene known to be associated with OPMD. Confirmatory molecular diagnosis of both autosomal dominant and autosomal recessive OPMD depends upon detection of an expansion of a GCN trinucleotide repeat in the first exon of *PABPN1*. Such testing is available clinically. Normal alleles contain ten GCG trinucleotide repeats [i.e., $(GCN)_{10}$]. Autosomal dominant alleles range in size from 12 to 17 GCN repeats [i.e., $(GCN)_{12\text{-}17}$]. Autosomal recessive alleles contain 11 GCN repeats [i.e., $(GCN)_{11}$]. Muscle biopsy is warranted only in individuals with suspected OPMD who have two normal *PABPN1* alleles.

Management. Treatment for ptosis may include blepharoplasty - either resection of the levator palpebrea aponeurosis or frontal suspension of the eyelids. Treatment for dysphagia may include surgical intervention in the presence of very symptomatic dysphagia, marked weight loss, near-fatal choking (which is extremely rare), or recurrent pneumonia. Cricopharyngeal myotomy alleviates symptoms in most cases. Dysphagia reappears slowly over years in many individuals. Contraindications to surgery are severe dysphonia and lower esophageal sphincter incompetence. The frequency of the follow-up neurological evaluations depends on the degree of ptosis, dysphagia, and muscle weakness. Ophthalmological evaluation should be performed when ptosis interferes with driving or is associated with neck pain or when the eyelids cover more than 50% of the pupils. Swallowing evaluation and surgical consultations are requested when dysphagia becomes cumbersome.

Genetic counseling. Oculopharyngeal muscular dystrophy is inherited in either an autosomal dominant or an autosomal recessive manner. For autosomal dominant OPMD, the risk to each sib of inheriting the mutation is 50% if a proband has an expanded $(GCN)_{12\text{-}17}$. Each child of an individual heterozygous for one expanded allele $(GCN)_{12\text{-}17}$ has a 50% chance of inheriting the disease-causing mutation. A proband with autosomal dominant OPMD may have the disorder as the result of a *de novo* mutation. The proportion of cases caused by de novo mutations is unknown, but appears to be small. A single case of an individual with autosomal recessive OPMD who was homozygous for the $(GCG)_{11}$ allele has been reported. The offspring of an individual with autosomal recessive OPMD are obligate heterozygotes (carriers) for a mutant allele causing OPMD. The risk of the child being affected is less than 1%. Prenatal testing is technically possible for pregnancies at risk if molecular genetic testing of the affected parent has revealed the GCG triplet repeat in the *PABPN1* gene; however, requests for prenatal testing for adult-onset conditions such as OPMD that do not affect intellect or life span, result in relatively mild physical limitations, and require that the asymptomatic at-risk parent be tested to confirm the at-risk status of the fetus are very uncommon.

Diagnosis

Clinical Diagnosis

Autosomal dominant oculopharyngeal muscular dystrophy (OPMD). The following three criteria are required for a diagnosis of autosomal dominant OPMD:

- A positive family history with involvement of two or more generations
- The presence of ptosis (defined as either vertical separation of at least one palpebral fissure that measures less than 8 mm at rest) OR previous corrective surgery for ptosis
- The presence of dysphagia, defined as swallowing time greater than seven seconds when drinking 80 mL of ice-cold water [Brais et al 1995]

Autosomal recessive OPMD. The symptoms and signs are the same as for autosomal dominant OPMD, but appear during the sixties, whereas they generally appear earlier in the autosomal dominant form (see Natural History section). The family history is consistent with autosomal recessive inheritance (i.e., affected sibs without affected parents and/or parental consanguinity).

Testing

Muscle biopsy. Previously the diagnosis of OPMD was based on the presence of intranuclear inclusions (INI) on muscle biopsy; now muscle biopsy is only warranted in those individuals with normal results on molecular genetic testing. The OPMD intranuclear inclusions consist of tubular filaments [Tomé & Fardeau 1980]. The filaments are up to 250 nm in length and have an external diameter of 8.5 nm and an internal diameter of 3 nm. Of the nuclei seen in

every ultra-thin section of deltoid muscle, 4% to 5% contain intranuclear inclusions [Tomé & Fardeau 1980]. The percentage of nuclei with inclusions is thought to correlate mostly with the limited volume that they occupy [Tomé et al 1997]. Other non-specific pathological findings include rimmed vacuoles and small angulated muscle fibers [Tomé et al 1997].

Electromyography (EMG) of weak muscles usually reveals discrete signs of a myopathic process [Bouchard et al 1997]. Very mild neuropathic findings have been reported, but are thought to be related in most cases to old age or concomitant disease.

Serum CK concentration elevated two to seven times the normal value has been reported in individuals with OPMD with severe leg weakness [Barbeau 1996]. In most cases, however, serum CK concentration is normal or up to twice the upper normal value.

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. *PABPN1*, encoding the polyadenylate binding protein nuclear 1, is the only gene known to be associated with OPMD. (*PABPN1* was previously called *PABP2*.)

The molecular diagnosis of autosomal dominant and autosomal recessive OPMD depends upon detection of larger than normal "GCN" trinucleotide repeat in the first exon of *PABPN1* [Brais et al 1998]. Note: Since all four codon combinations — GCA, GCT, GCC, and GCG — encode the amino acid alanine, the term "GCN" is the generic designation for any one of these four possible codons. In the designation of mutations, it is appropriate to either give the sequence of the mutation or more practically refer to the normal allele $(GCN)_{10}$ and the abnormal alleles $(GCN)_{11\text{-}17,}$ which is reminiscent of the classification of mutations in other triplet expansion diseases.

- **Normal alleles:** Ten GCN repeats $(GCN)_{10}$ (previously referred to as the $(GCG)_6$ normal allele).

Note: The *PABPN1* mutations were first described as pure (GCG) expansions of a $(GCG)_6$ stretch coding for six alanines in the first exon of the gene [Brais et al 1998]. However, it has become clear that approximately 25% of these mutations consist of (GCN) insertions or cryptic synonymous expansions [Nakamoto et al 2002] that do not modify the impact on the PABPN1 protein because all four (GCN) triplets code for alanine.

- **Autosomal dominant alleles:** Twelve to 17 GCN repeats $(GCG)_{12\text{-}17}$]. The percentage of families sharing the different mutations is [Brais et al 1998]:
  - 5% $(GCG)_{12}$
  - 40% $(GCG)_{13}$
  - 26% $(GCG)_{14}$
  - 21% $(GCG)_{15}$
  - 7% $(GCG)_{16}$
  - 1% $(GCG)_{17}$

- **Autosomal recessive alleles:** Eleven GCN repeats $(GCN)_{11}$ (i.e., previously referred to as $(GCN)_7$). Autosomal recessive inheritance has only been observed in one instance in an individual homozygous for two $(GCN)_{11}$ alleles [Brais et al 1998].

Molecular genetic testing: Clinical uses

- Diagnostic testing for autosomal and recessive OPMB
- Diagnostic testing for compound heteroyzygotes for dominant and recessive OPMD
- Presymptomatic testing (technically available although rarely performed)
- Prenatal diagnosis (technically available although rarely performed)

*The policy of *GeneReviews* is to include clinical uses of testing that is available from laboratories listed in the GeneTests Laboratory Directory regardless of whether the author(s)/editor(s)/reviewer(s) endorse these uses.

Molecular genetic testing: Clinical method

- **Targeted mutation analysis.** Testing to determine the size of the GCN trinucleotide repeat in the first exon of *PABPN1* is more than 99% sensitive and 100% specific. Growing evidence indicates that more than 99% of individuals with a severe dominant OPMD-like phenotype have a *PABPN1* (GCN) expansion.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Oculopharyngeal Muscular Dystrophy (OPMD)

Test Method	Mutation Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis	Heterozygosity for $(GCN)_{12\text{-}17}$	>99%, autosomal dominant	Clinical Testing
	Homozygosity for $(GCN)_{11}$	>99%, recessive [1]	

1. One case reported [Brais et al 1998]

Testing Strategy for a Proband

Molecular genetic testing is used to confirm the diagnosis individuals known or suspected to have OPMD. Muscle biopsy is warranted only in individuals with suspected OPMD who have two normal *PABPN1* alleles.

Genetically Related (Allelic) Disorders

No other diseases are known to be caused by mutations in the *PABPN1* gene.

Clinical Description

Natural History

Autosomal dominant OPMD. The age of onset of autosomal dominant OPMD is variable and often difficult to pinpoint. In a study of 72 French-Canadian symptomatic individuals with a $(GCN)_{13}$ mutation, the mean age of onset for ptosis was 48.1 years (range 26-65 years) and for dysphagia was 50.7 years (range 40-63 years).

Early symptoms that are suggestive of dysphagia caused by OPMD are an increased time needed to complete a meal and an acquired avoidance of dry foods. Other signs observed as the disease progresses are tongue atrophy and weakness (82%), proximal lower extremity weakness (71%), dysphonia (67%), limitation of upward gaze (61%), facial muscle weakness (43%), and proximal upper extremity weakness (38%) [Bouchard et al 1997].

Severity of the autosomal dominant OPMD phenotype is variable. Severe cases represent 5% to 10% of all cases. These individuals have earlier onset of ptosis and dysphagia (before the age of 45 years) and an incapacitating proximal leg weakness that starts before age 60 years. Some of these individuals eventually need a wheelchair. OPMD does not appear to reduce life span but quality of life in later years is greatly diminished [Becher et al 2001].

Autosomal recessive OPMD. Ptosis and dysphagia occur after age 60 years. There is some evidence suggesting that heterozygous carriers of the recessive $(GCG)_7$ allele may be at higher risk of developing dysphagia after the age of 70 years.

Genotype-Phenotype Correlations

The variability of age of onset and severity of weakness may depend on the size of the $(GCN)_n$ mutations, but this important issue is still unresolved.

- Severe autosomal dominant OPMD. Twenty percent of individuals with more severe autosomal dominant OPMD have inherited an allele in the $(GCN)_{12\text{-}17}$ range and a polymorphism in the other *PABPN1* allele that causes the insertion of one extra GCN triplet, thus producing the $(GCN)_{11}$ recessive allele [Brais et al 1998]. This polymorphism has 1% to 2% prevalence in North America, Europe, and Japan.
- The cause of the increased severity in the other 80% of individuals with severe autosomal dominant OPMD is unknown. Severely affected individuals cluster in families, a phenomenon suggesting that other genetic factors modulate severity.
- The most severe OPMD presentation is reported for individuals who are homozygotes for an autosomal dominant OPMD mutation [Blumen et al 1996, Brais et al 1998, Blumen et al 1999]. A study of four French-Canadian and three Bukhara Jewish OPMD homozygotes documented that on average the onset was 18 years earlier than in $(GCN)_{13}$ heterozygotes.
- Individuals with autosomal recessive OPMD (i.e., caused by homozygosity for $(GCN)_{11}$ alleles) have a later onset and milder disease.

Penetrance

The decade-specific cumulative penetrance for individuals with an autosomal dominant $(GCN)_{13}$ mutation is [Brais et al 1997]:

- Age <40 years: 1%
- Age 40-49 years: 6%
- Age 50-59 years: 31%
- Age 60-69 years: 63%
- Age >69 years: 99%

Therefore, autosomal dominant $(GCN)_{13}$ OPMD is fully penetrant past age 70 years.

Anticipation

The GCN/alanine triplet repeat in *PABPN1* is mitotically and meiotically stable. Therefore,expansion of the triplet repeat in meiosis is rare. Clinical anticipation is not observed with this disease. The estimated secondary mutation of an existent dominant mutation is in the order of 1:500 meioses [Brais et al 1998].

Prevalence

Autosomal dominant. The prevalence of OPMD has been estimated to be 1:100,000 in France, 1:1000 in the French-Canadian population of the province of Quebec, and 1:600 among Bukhara Jews living in Israel [Brais et al 1995, Blumen et al 1997, Brunet et al 1997]. In the United States, the majority of affected individuals are of French-Canadian extraction, though a large number are also of other backgrounds, including Jewish Ashkenazi [Victor et al 1962] and Spanish American in Texas [Becher 2001] and California [Grewal et al 1999].

Autosomal dominant OPMD has been identified in individuals from more than 30 countries.

Autosomal recessive. The predicted prevalence of the autosomal recessive form should be in the order of 1:10,000 in France, Quebec, and Japan based on the allele frequency of the $(GCN)_{11}$ autosomal recessive mutation in these populations [Brais et al 1998].

Differential Diagnosis

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

The differential diagnosis includes:

Myotonic dystrophy type 1 and myotonic muscular dystrophy type 2

Autosomal dominant distal myopathy

- Distal herditary motor neuropathy type VII (HMN7; Harper-Young yyopathy) (OMIM 158580). In these families spinal muscular atrophy is accompanied by vocal cord and pharyngeal weakness without ptosis [Young & Harper 1980]. McEntagart et al (2001) mapped this disorder to 2q14.
- Feit et al1998 described a distal myopathy with a similar phenotype of vocal cord and pharyngeal dysfunction (OMIM 606070), which maps to chromosome 5q31.

Mitochondrial myopathy with or without progressive external ophthalmoplegia (PEO) including mitochondrial neurogastrointestinal encephalomyopathy disease (MNGIE syndrome)

Myasthenia gravis. The absence of family history and the fluctuation of symptoms in myasthenia gravis usually distinguish the two conditions. If in doubt, electromyography and neostigmine testing can confirm the diagnosis of myasthenia gravis, and molecular genetic testing can confirm the diagnosis of OPMD.

Polymyositis and progressive bulbar palsy. These conditions do not have ptosis.

Blepharophimosis, ptosis, and epicanthus inversus (See *GeneReview* on Blepharophimosis, Ptosis, and Epicanthus Inversus. In this condition, the ptosis is usually congenital, it is always associated with epicanthus inversus, and dysphagia is not a feature.

Congenital fibrosis of the extraocular muscles. See *GeneReview* entitled Congenital Fibrosis of the Extraocular Muscles.) In this condition, the ptosis is congenital and dysphagia is not a feature.

Other At least one other dominant OPMD-like condition, which is more severe and is not caused by GCN expansion mutations in the *PABPN1* gene, appears to exist [Hill et al 2004].

Oculopharyngodistal myopathy (OMIM 164310) is still a poorly characterized condition in which dysphagia, ptosis, and distal weakness appear earlier in the twenties than in OPMD. The mode of transmission is still unclear; both dominant and recessive modes have been proposed. Pathologically no intranuclear inclusions are observed and no (GCN) *PABPN1* mutations are observed [van der Sluijs et al 2004].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Evaluation for swallowing difficulties by history and in more severe cases with swallowing studies.
- Neurological evaluation to establish the presence of ptosis, dysphagia, and proximal weakness and to exclude the presence of other neurological findings.
- EMG and muscle biopsy, required only in cases with more severe complicated presentations

Treatment of Manifestations

Ptosis.

- Surgery is recommended when the ptosis interferes with vision or appears to cause cervical pain secondary to constant dorsiflexion of the neck.
- Two types of blepharoplasty are used to correct the ptosis: resection of the levator palpebrae aponeurosis and frontal suspension of the eyelids [Codere 1993].
- Resection of the aponeurosis is easily done, but usually needs to be repeated once or twice [Rodrigue & Molgat 1997].
- Frontal suspension of the eyelids uses a thread of muscle fascia as a sling; the fascia is inserted through the tarsal plate of the upper eyelid and the ends are attached in the frontalis muscle, which is relatively preserved in OPMD [Codere 1993]. The major advantage of frontal suspension of the eyelids is that it is permanent; however, the procedure requires general anesthesia.

Dysphagia.

- Although there have been no controlled trials [Hill et al 2004], surgical intervention for dysphagia should be considered in the presence of very symptomatic dysphagia, marked weight loss, near-fatal choking (which is extremely rare), or recurrent pneumonia [Duranceau et al 1983].
- Cricopharyngeal myotomy alleviates symptoms in most cases [Duranceau et al 1983]. This surgery usually requires overnight hospitalization and a one-week convalescence. Dysphagia reappears slowly over years in many cases. Contraindications to surgery are severe dysphonia and lower esophageal sphincter incompetence [Duranceau 1997].

Prevention of Secondary Complications

The major complications of OPMD are aspiration pneumonia, weight loss, and social withdrawal because of frequent choking while eating.

To reduce these risks, the following are recommended:

- Annual flu vaccination is recommended for elderly affected individuals

- Consultation should be sought promptly for a productive cough because of the increased risk for lung abscesses.
- Dietary supplements should be added if weight loss is significant.
- Food should be cut into small pieces.
- To diminish social withdrawal, when attending meals with family and friends, affected individuals should be encouraged to either not eat or choose a dish they can swallow easily.

General anesthesia is not contraindicated even though individuals with OPMD may respond differently to certain anesthetics [Caron et al 2005].

Surveillance

The frequency of the follow-up neurological evaluations depends on the degree of ptosis, dysphagia, and muscle weakness.

Ophthalmological evaluation should be performed when ptosis interferes with driving or is associated with neck pain or when the eyelids cover more than 50% of the pupils.

Swallowing evaluation and surgical consultations are requested when dysphagia becomes cumbersome.

Therapies Under Investigation

Repetitive dilatations of the upper-esophageal sphincter with bougies is still under investigation [Mathieu et al 1997].

Botulium toxin injection of the cricopharyngeal muscle may be an alternative treatment, although no large control study has been published [Restivo et al 2000].

A trial of myoblast injection into the cricopharyngeal muscle to alleviate dysphagia is underway in France.

In cellular models of OPMD, investigators have reduced cellular toxicity by inducing heat shock protein expression using ZnSO4, 8-hydroxyquinoline, ibuprofen, and indomethacin [Wang et al 2005] or exposing cells to anti-PABPN1 antibodies that interfere with oligomerization [Verheesen et al 2006].

In a transgenic model of OPMD, investigators have reduced inclusion formation and cell death with agents that interfere with protein aggregation such as doxycycline [Davies et al 2005] and trehalose [Davies et al 2006]. These studies suggest that therapeutic trials in OPMD are possible given that some of the tested molecules have already been given to humans.

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

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

Oculopharyngeal muscular dystrophy is inherited in either an autosomal dominant or an autosomal recessive manner.

Risk to Family Members — Autosomal Dominant OPMD

Parents of a proband

- Most individuals diagnosed with OPMD have at least one affected parent.
- A proband with OPMD may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is unknown but appears to be small.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include clinical evaluation and/or molecular genetic testing.

Note: Although most individuals diagnosed with OPMD have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms or late onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs of the proband depends upon the status of the parents.
- If a parent of the proband has an expanded (GCN) allele, the risk to the sibs of inheriting the mutation is 50%.

Offspring of a proband

- **Heterozygotes.** Each child of an individual heterozygous for one expanded allele $(GCN)_{12\text{-}17}$ has a 50% chance of inheriting the disease-causing mutation.
- **Homozygotes.** A few individuals (French Canadians and members of the inbred population of Bukhara Jews living in Israel [Blumen et al 1999]) who are homozygous for the alleles $(GCN)_{13}$ have been described. All children of such a person will be heterozygous for the dominant mutation.

Other family members of the proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected, the proband's family members are at risk.

Risk to Family Members — Autosomal Recessive OPMD

A single case of an individual homozygous for the $(GCN)_{11}$ allele has been reported [Brais et al 1998]. This single individual has been referred to as having autosomal recessive OPMD. Because the $(GCN)_{11}$ allele has a 1% to 2% prevalence, other persons who are homozygous for this allele with a mild OPMD phenotype may be unrecognized because of a negative family history.

Parents of a proband

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

- Parents of individuals with autosomal recessive OPMD are unlikely to be alive at the time of diagnosis of their child and should not have been affected.

Sibs of a proband

- At conception, each sib of an affected individual has 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 chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are usually asymptomatic.

Offspring of a proband. The offspring of an individual with autosomal recessive OPMD are obligate heterozygotes (carriers) for a mutant allele causing OPMD. The risk of the child being affected is less than 1%.

Other family members of a proband. Sibs of the proband's parents are at 50% risk of also being carriers.

Carrier Detection

Carrier testing is technically available on a clinical basis once the diagnosis has been established in the proband by molecular genetic testing. Please refer to Molecular Genetic Testing above.

Related Genetic Counseling Issues

Specific risk issues. Individuals inheriting an autosomal dominant mutation from an affected parent and an autosomal recessive mutation [$(GCN)_{11}$] from the other parent will develop a severe form of OPMD.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.

Testing of at-risk asymptomatic adults for OPMD is available using the same techniques described in Molecular Genetic Testing. This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. When testing at-risk individuals for OPMD, an affected family member should be tested first to confirm that the disorder in the family is actually OPMD.

Testing for the disease-causing mutation in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations, including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pre-test interviews in which the motives for requesting the test, the individual's knowledge of OPMD, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long term follow-up and evaluations.

Testing of at-risk individuals during childhood. Consensus holds that individuals at risk for adult-onset disorders should not have testing during childhood in the absence of symptoms. The principal arguments against testing individuals during childhood who do not have symptoms are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications [Bloch & Hayden 1990, Harper & Clarke 1990]. Individuals who are symptomatic during childhood usually benefit from having a specific diagnosis established. See also the National Society of Genetic Counselors' resolution on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents.

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. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis* for pregnancies at increased risk is technically possible but uncommonly requested. DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation is analyzed. The disease-causing expansion must be identified in an affected family member before prenatal testing can be performed.

*The policy of *GeneReviews* is to include information on prenatal testing that is available from laboratories listed in the GeneTests Laboratory Directory regardless of whether the author(s)/editor(s)/reviewer(s) endorse its use.

Requests for prenatal testing for adult-onset conditions such as OPMD that do not affect intellect or life span, result in relatively mild physical limitations, and require that the asymptomatic at-risk parent be tested to confirm the at-risk status of the fetus are very uncommon. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

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

Molecular Genetics

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

Table A. Molecular Genetics of Oculopharyngeal Muscular Dystrophy

Gene Symbol	Chromosomal Locus	Protein Name
PABPN1	14q11.2-q13	Polyadenylate-binding protein 2

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 Oculopharyngeal Muscular Dystrophy

164300	OCULOPHARYNGEAL MUSCULAR DYSTROPHY; OPMD
602279	POLYADENYLATE-BINDING PROTEIN, NUCLEAR, 1; PABPN1

Table C. Genomic Databases for Oculopharyngeal Muscular Dystrophy

Gene Symbol	Entrez Gene	HGMD
PABPN1	8106 (MIM No. 602279)	PABPN1

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

Normal allelic variants: *PABPN1* has seven exons. The role of the two long introns preserved in many of its mRNAs is unknown.

Pathologic allelic variants: See Molecular Genetic Testing.

The OPMD mutations expand a $(GCN)_n$ sequence that immediately follows the start ATG. As in (CAG)/polyglutamine diseases, it is the absolute size of the domain that is the size of the mutation and not the size of the added expansions. It is not known for sure if the mutation mechanism is expansion of the GCN repeat through slippage or insertion of additional $(GCN)_n$ through unequal recombination or gene conversion events [Chen et al 2005].

Normal gene product: PABPN1 protein has at least the following six domains: polyalanine, coil-coiled, RNA binding, and two oligomerization and a nuclear localization signal (NLS) [Calado et al 2000, Fan et al 2001, Kuhn et al 2003]. PABPN1 is an abundant nuclear protein of ~49 kDa that binds with high affinity to nascent poly(A) tails at the 3' end of mRNAs [Wahle et al 1993, Nemeth et al 1995]. The poly(A) tail is post-transcriptionally added to the mRNA by a number of trans-acting factors including PABPN1, the cleavage and polyadenylation specificity factor (CPSF), and the poly(A) polymerase (PAP) [Wahle & Ruegsegger 1999, Zhao et al 1999].

It was demonstrated that PABPN1 shuttles between nucleus and cytoplasm [Calado et al 2000]. PABPN1 is associated with RNA polymerase II during transcription and accompanies the released transcript though the nuclear pore [Bear et al 2003, Kerwitz et al 2003]. Nuclear export of PABPN1 is temperature-sensitive, and depends on RNA binding and ongoing transcription. Nuclear import of PABPN1 is an active transportin-mediated process [Calado et al 2000].

Several PABPN1 binding partners have been identified to date. These include the heterogeneous family members HNRPA/B, HNRPA1 [Fan et al 2003] and HNRPC [Calapez et al 2002]. By immunoprecipitation, PABPN1 was found to interact with proteins of the cap-binding complex (CBP80, CBP20, and EIF4G) and with proteins involved in mRNA decay (Upf2 and Upf3) [Ishigaki et al 2001]. PABPN1-interacting partners also include HSP40 (DNAJ) and BRG1 [Kim et al 2001]. Finally, PABPN1 has been shown to interact with SKIP and to stimulate muscle-specific gene expression when overexpressed [Kim et al 2001].

Abnormal gene product: Various hypotheses of a polyalanine toxicity gain-of-function pathogenetic mechanism have been proposed [Brais et al 1998, Brais et al 1999]. Abnormal aggregation and inefficient protein degradation are some of the gain-of-function pathological mechanisms proposed [Brais 2003]. In these models, PABPN1 is thought to have a pathogenic expanded polyalanine domain with physical characteristics that cause it to accumulate and interfere with normal cellular processes. However, despite the growing number of studies

exploring OPMD pathogenesis, the nature of the underlying pathological mechanism has yet to be established.

- **Accumulation/aggregation.** It was proposed that when more than ten alanines (the normal number) are present in PABPN1, the polyalanine domains polymerize to form stable β-sheets that are resistant to nuclear proteosomal degradation. The polyalanine macromolecules grow with time to form the OPMD PABPN1-containing intranuclear filaments that are seen on electron microscopy [Tomé & Fardeau 1980, Tomé et al 1997, Calado et al 2000].

  Various fusion proteins with long polyalanine domains accumulate as intranuclear inclusions (INI) [Gaspar et al 2000, Rankin et al 2000]. In one transfection experiment, a long 37-Ala-GFP fusion protein caused nuclear inclusion formation and cell death [Rankin et al 2000].

  Studies with agents that influence this aggregation have been explored and in most cases improve outcome in cellular and mice models of OPMD [Davies et al 2005, Wang et al 2005, Davies et al 2006, Verheesen et al 2006].

- **Inefficient protein degradation.** Evidence suggesting that polyalanine oligomers form resistant macromolecules in vivo and in vitro includes the following:

  - Polyalanine oligomers are known to be resistant to protease digestion or chemical degradation [Forood et al 1995].
  - Polyalanine oligomers form a β-sheet structure in vitro [Forood et al 1995].
  - Polyalanine oligomers containing more than eight alanines in a row form fibrils spontaneously [Blondelle et al 1997].

PABPN1 molecules in the intranuclear inclusions (INI) of OPMD muscle are more resistant to salt extraction than the protein dispersed in the nucleoplasm [Calado et al 2000].

- **mRNA trapping** is another proposed pathophysiological hypothesis [Galvao et al 2001]. It has been shown that to aggregate and cause toxicity, PABPN1 has to enter the nuclei [Abu-Baker et al 2005]. Inclusion formation and PABPN1 inclusions have broad and significant impact on the expression of numerous genes, in particular ones that are involved in mRNA processing [Corbeil-Girard et al 2005].

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.

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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

Dystrophie musculaire oculopharyngie, Monographie Myoline, Association Française contre les myopathies (AFM), June 1995 (in French)

American Society of Human Genetics and American College of Medical Genetics (1995) Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents

National Society of Genetic Counselors (1995) Resolution on prenatal and childhood testing for adult-onset disorders

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Chapter Notes

Revision History

- 22 June 2006 (ca) Comprehensive update posted to live Web site
- 3 December 2003 (me) Comprehensive update posted to live Web site
- 8 March 2001 (me) Review posted to live Web site
- December 2000 (bb) Original submission