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Polycystic Lipomembranous Osteodysplasia with Sclerosing Leukoencephalopathy (PLOSL)

[*Membranous Lipodystrophy, Nasu-Hakola Disease, Polycystic Lipomembranous Osteodysplasia with Sclerosing Leukoencephalopathy*]

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Summary

Disease characteristics. Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) is characterized by fractures resulting from radiologically demonstrable polycystic osseous lesions, frontal lobe syndrome, and progressive presenile dementia beginning in the fourth decade. The clinical course of PLOSL can be divided into four stages: (1) The latent stage is characterized by normal early development. (2) The osseous stage (third decade of life) is characterized by pain and tenderness, mostly in ankles and feet, usually following strain or injury. Fractures are typically diagnosed several years later, most commonly in the bones of the extremities. (3) In the early neurologic stage (fourth decade of life), a change of personality begins to develop insidiously. Affected individuals show a frontal lobe syndrome (loss of judgment, euphoria, loss of social inhibitions, disturbance of concentration, and lack of insight, libido, and motor persistence), leading to serious social problems. (4) The late neurologic stage is characterized by progressive dementia and loss of mobility. Death usually occurs by age 50 years.

Diagnosis/testing. The combination of radiologically demonstrable polycystic osseous lesions, frontal lobe syndrome, and progressive presenile dementia beginning in the fourth decade is diagnostic. Fractures of the wrists or ankles after minor trauma with typical polycystic osseous lesions identified on x-ray examination suggest the possibility of PLOSL. In uncertain cases, molecular genetic testing helps to establish the diagnosis. *TYROBP(DAP12)* and

TREM2 are the two genes associated with PLOSL. Molecular genetic testing of *TYROBP* and *TREM2*, avilable on a research basis only, is likely to detect mutations in 100% of affected individuals. All Finnish individuals with PLOSL are homozygous for a deletion of exons 1-4 of *TYROBP*.

Management. Treatment is symptomatic. Orthopedic surgery and/or devices may be of value in individual cases. Antiepileptic drugs can prevent worsening of the condition. Surveillance intervals for bone lesions and neurologic and psychiatric manifestations must be determined individually.

Genetic counseling. PLOSL is inherited in an autosomal recessive manner. 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 testing may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

The combination of the following features is diagnostic of polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL):

- **Radiologically demonstrable polycystic osseous lesions** and fractures of the wrists or ankles after minor trauma. Cyst-like lesions and trabecular loss are most conspicuous in the fingers and in the carpal and tarsal bones [Makela et al 1982].
- **Frontal lobe syndrome** in the fourth decade manifested by euphoria and loss of judgment and social inhibitions
- **Progressive presenile dementia** beginning in the fourth decade. Dementia is mild at the onset of neurologic symptoms. The disease culminates in severe dementia; affected individuals typically die by age 50 years.

Testing

Bone biopsy. The cyst-like bone lesions are filled with lipid material that microscopically consists of characteristic 1-2 µm-thick lipid membranes and amorphous lipid substance [Nasu et al 1973, Akai et al 1977, Kitajima et al 1989].

Neuroradiologic examination

- **Cerebral atrophy** (dilated ventricles and prominent sulci) of varying degree is a constant finding on CT and MRI and is evident even before the appearance of neuropsychiatric symptoms. In addition to progressive cerebral atrophy, cerebellar atrophy may appear [Araki et al 1991, Hakola & Puranen 1993, Paloneva et al 2001].
- **Bilateral calcifications of the basal ganglia** are a common finding on CT. Most often, they are situated in the putamina. Calcifications, atrophy of the basal ganglia, and progressively increasing and abnormally high bicaudate ratios may occur before CNS symptoms [Bird et al 1983, Araki et al 1991, Hakola & Puranen 1993, Paloneva et al 2001]. The basal ganglia, particularly the putamina, may show very low signal intensities on T2-weighted MR images [Araki et al 1991, Paloneva et al 2001].
- **Increased signal intensities of the cerebral white matter** are usually found on T2-weighted images after the appearance of clinical CNS symptoms. These white matter changes are diffuse and have no region of predilection, apart from the frontal lobes.

The lesions are usually centrally located, sparing most of the arcuate fibers. In some instances, they also extend to the cortex. However, the white matter may look normal in some individuals with CNS symptoms [Paloneva et al 2001].

- **SPECT findings** are variable. Hypoperfusion of the cortical areas, thalamus, and basal ganglia have been reported [Takeshita et al 2005, Klunemann et al 2005].

Electroencephalogram. EEG is normal early in the disease. With advancing disease, individuals show accentuation of theta and delta activity. Initially, theta is typically rhythmic, 6-8 Hz, dominating in the centrotemporal areas; later, diffuse slowing becomes evident. In the late stage of the disease, irritative activity usually appears in the EEG [Bird et al 1983, Hakola & Partanen 1983, Motohashi et al 1995, Paloneva et al 2001].

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—Genes. *TYROBP(DAP12, KARAP*) and *TREM2* are the only genes known to be associated with PLOSL. Mutations in these two genes are likely to be responsible for PLOSL in 100% of affected individuals. In individuals outside of Finland and Japan, *TREM2* appears to be mutated more frequently than *TYROBP* [Klunemann et al 2005].

Molecular genetic testing: Research. All affected individuals tested to date are homozygous for their disease-causing mutation; compound heterozygotes have not been reported.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in PLOSL

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Direct DNA [1]	*TYROBP* [2] Deletion of exons 1-4	100% of Finnish individuals, unknown portion of Swedish and Norwegian individuals	Research only
	TYROBP 141delG	Unknown portion of Japanese individuals	
	TYROBP 2T>C	Two Japanese families	
	TREM2 [2] 233G>A	Two Swedish families	
	TREM2 377T>G	One Canadian and British family (both originating from Sri Lanka)	

1. The use of mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with a specific disorder

2. Only mutations reported in more than one family are presented. Most of the mutations found outside Finland and Japan were previously unknown and are found in single families.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be caused by mutations in either *TYROBP* or *TREM2*.

Clinical Description

Natural History

The clinical course of polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) can be divided into four stages: latent, osseous, early neurologic, and late neurologic [Hakola 1972, Hakola 1990a, Paloneva et al 2001, Klunemann et al 2005].

1. **Latent stage.** Early development is normal.
2. **Osseous stage (third decade of life).** The first symptoms of PLOSL appear in early adulthood as pain and tenderness, mostly in the ankles and feet, usually following strain or a minor accident. Fractures are typically diagnosed several years later, most commonly in the bones of the extremities [Makela et al 1982, Paloneva et al 2001]. The first fractures usually occur shortly before age 30 years; however, affected individuals may have been experiencing pain and swelling of the ankles and wrists after strain for years. The fractures heal well. It is important to note that some individuals may present with neurologic symptoms without any preceding osseous problems [Matsuo et al 1982, Paloneva et al 2001].
3. **Early neurologic stage (fourth decade of life).** Personality changes begin insidiously in the fourth decade. Affected individuals show progressive loss of judgment, leading to serious social consequences, including divorce, unemployment, and financial trouble [Hakola 1990b, Paloneva et al 2001]. Some individuals may attempt suicide. The full-blown picture of frontal lobe syndrome subsequently appears: loss of judgment, euphoria, lack of social inhibitions (including *Witzelsucht*), disturbance of concentration, and lack of insight, libido, and motor persistence.

   Progressive signs of upper motor neuron involvement (spasticity, extensor plantar reflexes) are noticed. With advancing disease, lack of initiative and activity conceal the aforementioned symptoms [Paloneva et al 2001].

   Memory disturbances begin at approximately the same age as the personality changes, and are best detectable by psychometric tests (Benton's Visual Retention Test, Ten-word test, and WMSc) [Hakola 1998]. The memory disturbance is less severe than the personality change, and affected individuals are able to retain the most important personal data until the last stage of the disease.

   Other disturbances of higher cortical function, such as motor aphasia, agraphia, acalculia, and apraxia, appear only at the last stage of the disease.

   Affected individuals may develop postural dyspraxia: they walk or sit in peculiar skewed postures. Involuntary athetotic or choreatic movements or myoclonic twitches are common. Individuals who reach their mid-thirties frequently experience epileptic seizures. In some individuals, impotence or lack of libido and urinary incontinence are among the first symptoms [Hakola 1972, Minagawa et al 1985, Ishigooka et al 1993, Paloneva et al 2001].
4. **Late neurologic stage.** In the last stage of the disease, individuals lose their ability to walk and progress to a vegetative state. Primitive reflexes, such as visual and tactile grasp and mouth-opening reflexes, as well as the sucking reflex, may become

noticeable. Individuals typically die by age 50 years [Verloes et al 1997, Paloneva et al 2001].

Neuropathology. Generalized cerebral gyral atrophy with frontal accentuation is observed at autopsy. The corpus callosum is abnormally thin. The central white matter is severely reduced in amount, greyish, and tough. The basal ganglia, particularly the caudate nuclei, are variably reduced in size [Paloneva et al 2001]. All affected individuals show marked *hydrocephalus e vacuo*.

Histologic examination reveals scattered neurons showing features of central chromatolysis. Intraneuronal or glial pathologic inclusions are not observed [Paloneva et al 2001]. Neuronal loss, astrocytic proliferation, and hypertrophy are observed in the caudate nuclei as well as scattered calcospherites, particularly in the putamina and globi pallidi [Amano et al 1987, Miyazu et al 1991, Kalimo et al 1994, Paloneva et al 2001]. Thalamic degeneration may occur [Tanaka 1980, Amano et al 1987, Miyazu et al 1991, Kobayashi et al 2000]. Affected individuals show advanced loss of axons and myelin and a pronounced astrocytic reaction in the centrum semiovale, accentuated in the frontal and temporal lobes, with moderate involvement of the gyral white matter. In addition, widespread activation of microglia in the cerebral white matter is seen [Paloneva et al 2001]. Scattered small arterioles and capillaries in the deep frontal and temporal white matter show concentric thickening of the vascular wall with multiple thickened basement membranes and narrowing or obliteration of the lumen [Kalimo et al 1994, Paloneva et al 2001].

Pathologic findings in other organs. Characteristic lipomembranous changes have been described in systemic adipose tissue [Nasu et al 1973]. Pathologic manifestations in organs other than the CNS and the skeletal system have been insufficiently characterized.

Genotype-Phenotype Correlations

All individuals with homozygous loss-of-function mutations in *TYROBP* or *TREM2* develop similar disease manifestations [Paloneva et al 2002, Klunemann et al 2005].

Nomenclature

PLOSL or Nasu-Hakola disease are the recommended names.

- Some authors have preferred the abbreviation "PLO-SL."
- The first affected individuals were described in the 1960s independently by Hakola in Finland and Nasu in Japan.

In the early literature, PLOSL was also known as membranous lipodystrophy. This term is outdated and should not be used.

Prevalence

The prevalence of PLOSL is highest in Finland with an estimated prevalence of 1-2 x 10^{-6} [Pekkarinen et al 1998]. The prevalence of PLOSL in other countries is lower than in Finland, and no detailed data on the prevalence elsewhere are available. Most affected individuals have been diagnosed in Japan (>100 cases) [Pekkarinen et al 1998]. Single families with PLOSL have been diagnosed worldwide [Klunemann et al 2005].

Differential Diagnosis

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

The combination of frontal-type dementia beginning in the fourth decade and radiologically demonstrable polycystic osseous lesions makes it easy to clinically distinguish PLOSL from the established forms of familial and non-familial frontotemporal dementia [Hardy & Gwinn-Hardy 1998, Dickson 1999] such as Pick's disease [Dickson 1998], nonspecific frontal lobe degeneration, and the various entities of frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) [Foster et al 1997], in several of which mutations of the *tau* (*MAPT)* gene have been reported [Hutton et al 1998, Spillantini et al 1998, Goedert et al 1999].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Radiographs of the bones of wrists, hands, ankles, and feet to determine the extent of osseous manifestations of the disease
- Brain CT and/or MRI to determine the extent of CNS manifestations
- Neurologic and neuropsychologic examination to establish the extent of neurologic impairment and cognitive disturbance

Treatment of Manifestations

Only symptomatic treatment is available.

Orthopedic ankle surgery as well as supportive orthopedic devices may be of value in individual cases. The fractures have been reported to heal well [Paloneva et al 2001].

Epileptic seizures may worsen the individual's condition. Consequently, adequate antiepileptic drugs (AEDs) are important.

Prevention of Primary Manifestations

No therapy to delay or halt the progression of the disease is known.

Prevention of Secondary Complications

Social problems (unemployment, divorce, financial troubles, and alcoholism) are often associated with the progression of the disease. Some of the social consequences may be avoided if family members are informed early about the nature of the disorder [Hakola 1990b].

Surveillance

The interval of surveillance for bone lesions and neurologic and psychiatric manifestations must be determined individually.

Testing of Relatives at Risk

In practice, only sibs of the affected individual who are under age 40 years are at risk.

Polycystic osseous lesions in radiographs of the hands and feet of an adult raise the suspicion of PLOSL.

Therapies Under Investigation

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

Other

Calcium substitution alone has been shown to be ineffective in preventing the development of the osseous manifestations. The effect of bisphosphonates has not been studied.

It has been speculated that nonsteroidal anti-inflammatory drugs (NSAIDs) slow the progression of PLOSL; however, clinical trials have not been performed.

A single individual with PLOSL improved temporarily when receiving donepezil [DM Hemelsoet, MD, personal observation]. Clinical trials in a series of individuals with PLOSL have not been reported.

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

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual 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. The offspring of an affected person are obligate heterozygotes. Because of the low carrier rate in the general population, the risk that an affected individual would have children with a carrier is very low except in genetic isolates.

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

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 PLOSL 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 or clinical laboratory. For laboratories offering custom prenatal testing, see Testing.

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 PLOSL

Gene Symbol	Chromosomal Locus	Protein Name
TREM2	6p21.2	Triggering receptor expressed on myeloid cells 2
TYROBP	19q13.1	TYRO Protein tyrosine kinase-binding protein

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 PLOSL

221770	POLYCYSTIC LIPOMEMBRANOUS OSTEODYSPLASIA WITH SCLEROSING LEUKOENCEPHALOPATHY; PLOSL
604142	TYRO PROTEIN TYROSINE KINASE-BINDING PROTEIN; TYROBP
605086	TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS 2; TREM2

Table C. Genomic Databases for PLOSL

Gene Symbol	Entrez Gene	HGMD
TREM2	54209 (MIM No. 605086)	TREM2
TYROBP	7305 (MIM No. 604142)	TYROBP

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

TREM2

Normal allelic variants: The *TREM2* gene consists of five exons and codes for a 693-bp cDNA. No normal allelic variants have been reported.

Pathologic allelic variants: Several homozygous mutations have been identified. Most individuals with *TREM2* mutations have a previously unknown mutation [Paloneva et al 2002, Paloneva et al 2003, Soragna et al 2003, Klunemann et al 2005]. Only mutations found in more than one family are presented here. For a list of all published mutations, see Klunemann et al (2005).

- **233G>A,** a mutation in the extracellular domain of *TREM2*, results in premature termination of translation with no transmembrane and cytoplasmic domains after 77 amino acids. The mutation has been reported in two Swedish families with PLOSL [Paloneva et al 2003].
- **377T>G,** a mutation in the extracellular domain of *TREM2*, results in conversion of V at position 126 to G. The mutation was found in one Canadian and one British individual with PLOSL, both originating from Sri Lanka [Klunemann et al 2005].

Normal gene product: The protein encoded by *TREM2* is 230 amino acids and is an activating cell-surface receptor that forms a complex with the transmembrane adaptor protein TYROBP (DAP12). TREM2 is expressed by a variety of cells of myeloid origin [Colonna 2003]. The natural ligand for TREM2 is unknown.

The TREM2-TYROBP protein complex regulates the differentiation and function of osteoclasts, the bone-resorbing cells [Paloneva et al 2003, Cella et al 2003, Humphrey et al 2005]. In the CNS, TREM2 is expressed by microglial cells [Colonna 2003, Kiialainen et al 2005]. The function of TREM2 in the CNS is unknown. TREM2 also activates monocyte-derived dendritic cells and is expressed by macrophages [Bouchon, Hernandez-Munain et al 2001; Colonna 2003].

Abnormal gene product: Depending on the type of mutation, the defective TREM2 protein is truncated, not translated, not transported to the cell surface, or the consequences of the mutation cannot be predicted.

The differentiation of osteoclasts is impaired in TREM2-deficient individuals, and the cells show a reduced bone resorption capability in vitro [Paloneva et al 2003, Cella et al 2003, Humphrey et al 2005].

TYROBP

Normal allelic variants: The *TYROBP* gene consists of five exons and codes for a 342-bp cDNA. No normal allelic variants have been reported.

Pathologic allelic variants: Several mutations have been identified. Three of them, deletion of exons 1-4, conversion of nucleotide T to C at position 2 (2T>C) and deletion of nucleotide 141 (141delG), have been found in more than one family with PLOSL [Paloneva et al 2000, Kondo et al 2002]. Other mutations reported in *TYROBP* have been found in single families only [Baeta et al 2002, Paloneva et al 2002, Klunemann et al 2005].

Deletion of exons 1-4. All Finnish individuals with PLOSL are homozygous for this deletion, which has also been found in Swedish and Norwegian families [Paloneva et al 2000, Tranebjærg et al 2000]. The 5.3-kb deletion encompasses the first four exons of *TYROBP*. No mRNA encoding DAP12 is produced.

- **2T>C,** a homozygous start methionine mutation, has been reported in two Japanese families with PLOSL [Kondo et al 2002]. This mutation results in conversion of the translation initiation methionine to threonine. No DAP12 polypeptide is produced.
- **141delG,** another homozygous mutation, has been found in a number of Japanese individuals with PLOSL. This single-base deletion creates a frameshift in the open reading frame (ORF), resulting in a premature termination of the polypeptide chain after 52 amino acids, and changes a functionally critical aspartic acid residue in the transmembrane domain. The defective protein is not transported to the cell surface [Paloneva et al 2000, Kondo et al 2002].

Normal gene product: The protein contains 113 amino acids and is a transmembrane adaptor protein that mediates the activation of a wide variety of cells of myeloid and lymphoid origin [Lanier, Corliss, Wu, Leong et al 1998; Bakker et al 1999; Bouchon et al 2000; Bouchon, Facchetti et al 2001]. On the cell plasma membrane, TYROBP is expressed as a disulfide-bonded homodimer linked to the associated cell surface receptors. Known *TYROBP*-associated cell surface receptors are: TREM1, TREM2 [Bouchon et al 2000], SIRP-BETA-1 [Dietrich et al 2000], NKp44 [Vitale et al 1998], MDL-1 [Bakker et al 1999], CD94 [Lanier, Corliss, Wu, Phillips 1998], KIR2DS2 [Lanier, Corliss, Wu, Leong et al 1998], NKG2C [Lanier, Corliss, Wu, Phillips 1998], and NKG2D [Diefenbach et al 2002, Gilfillan et al 2002]. The cytoplasmic domain of TYROBP contains an immunoreceptor tyrosine-based activation motif (ITAM) which, upon receptor engagement, becomes phosphorylated and binds the cytoplasmic protein tyrosine kinases SYK and ZAP70 [Lanier, Corliss, Wu, Leong et al 1998]. This interaction results in intracellular calcium mobilization and subsequent cellular activation [McVicar et al 1998].

The TYROBP-TREM2 protein complex regulates the differentiation and function of osteoclasts [Paloneva et al 2003, Humphrey et al 2004]. In the CNS, TYROBP is expressed by microglial cells, but the exact function of the protein in these cells is unknown [Kiialainen et al 2005, Takahashi et al 2005].

Abnormal gene product: Depending on the type of mutation, the defective TYROBP protein is either truncated, not translated, or not transported to the cell surface, or the consequences of the mutation cannot be predicted.

The differentiation of osteoclasts in TYROBP-deficient individuals is impaired and the osteoclasts show a reduced bone resorption capability in vitro [Paloneva et al 2003, Humphrey et al 2004].

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

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

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Suggested Readings

Chapter Notes

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