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Mitochondrial DNA Deletion Syndromes

[*mtDNA Deletion Syndromes. Includes: Kearns-Sayre Syndrome (KSS), Pearson Syndrome, Progressive External Ophthalmoplegia (PEO)*]

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Summary

Disease characteristics. Mitochondrial DNA (mtDNA) deletion syndromes comprise three overlapping phenotypes that may be observed in different members of the same family or may evolve in a given individual over time. The three phenotypes are Kearns-Sayre syndrome (KSS), Pearson syndrome, and progressive external ophthalmoplegia (PEO). KSS is a multisystem disorder defined by the triad of onset before age 20 years, pigmentary retinopathy, and PEO. In addition, affected individuals have at least one of the following: cardiac conduction block, cerebrospinal fluid protein concentration greater than 100 mg/dL, or cerebellar ataxia. Onset is usually in childhood. Pearson syndrome is characterized by sideroblastic anemia and exocrine pancreas dysfunction and is usually fatal in infancy. PEO, characterized by ptosis, paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness, is relatively benign.

Diagnosis/testing. Diagnosis of mtDNA deletion syndromes relies upon presence of characteristic clinical findings and, in KSS, changes on muscle biopsy [ragged-red fibers (RRF) with the modified Gomori trichrome stain, hyperactive fibers with the succinate dehydrogenase (SDH) stain, failure of both RRF and some non-RRF to stain with the histochemical reaction for cytochrome *c* oxidase (COX)] and decreased activity of respiratory chain complexes containing mtDNA-encoded subunits in muscle extracts. In Pearson syndrome, bone marrow examination reveals ringed sideroblasts, normoblasts with excessive deposits of iron in mitochondria detected by iron stains. Mitochondrial DNA deletion syndromes are caused by mtDNA deletions ranging in size from two to ten kilobases. Approximately 90% of individuals with KSS have a large-scale (i.e., 1.3-10 kb) mtDNA deletion that is usually present in all tissues; however, mutant mtDNA is often undetectable in blood cells, necessitating examination of muscle. In Pearson syndrome, mtDNA deletions are usually more abundant in blood than in other tissues. In PEO, mtDNA deletions are confined to skeletal muscle.

Management. Management of mtDNA deletion syndromes includes placement of cardiac pacemakers in individuals with cardiac conduction blocks, eyelid slings for severe ptosis, cochlear implants and hearing aids for neurosensory hearing loss, hormone replacement for endocrinopathies, dilation of the upper esophageal sphincter to alleviate cricopharyngeal achalasia, folinic acid supplementation in individuals with KSS with low CSF folic acid, replacement of pancreatic enzymes in Pearson syndrome, administration of coenzyme Q10 and

L-carnitine, physical and occupational therapy, and treatment of depression. Antioxidants may ameliorate damage from reactive oxygen species; percutaneous endoscopic gastrostomy may improve nutritional intake and prevent aspiration pneumonia in individuals with severe dysphagia. Surveillance includes EKG and echocardiogram every six to 12 months and yearly audiometry and endocrinologic evaluation.

Genetic counseling. Mitochondrial DNA deletion syndromes are caused by deletion of mtDNA and, when inherited, are transmitted by maternal inheritance. The father of a proband is not at risk of having the disease-causing mtDNA mutation. The mother of a proband with a mtDNA deletion syndrome is usually unaffected and does not have mtDNA deletions in her tissues; however, exceptions occur. The risk to the sibs of a proband is usually extremely low. Offspring of a female proband are usually not at risk of inheriting the mutation; however, exceptions occur. Offspring of males with a mtDNA mutation are not at risk. Prenatal testing is available on a clinical basis, although interpretation of results is difficult.

Diagnosis

Clinical Diagnosis

Mitochondrial DNA (mtDNA) deletion syndromes comprise the three following overlapping phenotypes, which may be observed in different members of the same family or may evolve in a given individual over time:

Kearns-Sayre syndrome (KSS) is a multisystemic disorder defined by the following obligatory triad:

- Onset before age 20 years
- Pigmentary retinopathy. Funduscopy reveals an atypical "salt and pepper" retinopathy. ERG findings have not been reported, and visual fields are normal.
- Progressive external ophthalmoplegia (PEO)

At least one of the following must also be present:

- Cardiac conduction block
- Cerebrospinal fluid protein concentration greater than 100 mg/dL
- Cerebellar ataxia [Kearns & Sayre 1958, Berenberg et al 1977, Rowland et al 1983]

Other frequent but not invariable clinical manifestations of KSS include short stature, hearing loss, dementia, limb weakness, diabetes mellitus, hypoparathyroidism, and growth hormone deficiency.

Pearson syndrome is a usually fatal disorder of infancy characterized by sideroblastic anemia and exocrine pancreas dysfunction [Rotig et al 1990].

Progressive external ophthalmoplegia (PEO) is a mitochondrial myopathy with drooping of the eyelids (ptosis), paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness.

A few individuals with PEO have other manifestations of KSS but do not fulfill all the clinical criteria for the diagnosis [Rowland et al 1983]. This situation is called "KSS minus" or "PEO plus."

Testing

Kearns-Sayre syndrome and progressive external ophthalmoplegia

- **Lactate and pyruvate concentrations** in blood and cerebrospinal fluid (CSF) are commonly elevated at rest and increase excessively in blood after moderate activity.
- **Electromyogram and nerve conduction studies** are consistent with a myopathy, but neuropathy may coexist.
- **Brain MRI** sometimes shows leukoencephalopathy, often associated with cerebral or cerebellar atrophy or basal ganglia lesions.
- **Fasting serum glucose concentration** to screen for diabetes mellitus
- **Echocardiogram and electrocardiogram** to evaluate cardiac conduction and contractility
- **Muscle biopsy** typically shows ragged-red fibers (RRF) with the modified Gomori trichrome stain and hyperactive fibers with the succinate dehydrogenase (SDH) stain. Both RRF and some non-RRF fail to stain with the histochemical reaction for cytochrome *c* oxidase (COX).
- **Biochemical studies of respiratory chain enzymes** in muscle extracts usually show decreased activities of respiratory chain complexes containing mtDNA-encoded subunits, especially when enzyme values are referred to the activity of citrate synthase, a good marker of mitochondrial "mass" [DiMauro et al 2002]. However, depending on the mutational load, biochemical studies may also be normal.

Pearson syndrome

- **Sideroblastic anemia** is defined by the presence of anemia and ringed sideroblasts in the bone marrow. Ringed sideroblasts are normoblasts with excessive deposits of iron in mitochondria and are detected by iron stains of bone marrow.
- **Exocrine pancreatic dysfunction** is manifest clinically by excessive fat excretion in the stools (steatorrhea), which can be documented qualitatively by Sudan staining of the feces or quantitatively by measuring fecal fat. The gold standard is the secretin stimulation test, which requires placing a catheter in the duodenum and is difficult to perform in infants.

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. Mitochondrial DNA deletions, ranging in size from two to ten kilobases, are associated with Kearns-Sayre syndrome, Pearson syndrome, and progressive external ophthalmoplegia.

- Over 150 different mtDNA deletions have been associated with KSS. A deletion of 4977 bp is encountered most frequently ("common deletion") [Schon 2003].
- The same 4977-bp deletion and numerous other types of deletions of varying length have been identified in Pearson syndrome and PEO.

Clinical uses

- Diagnostic testing
- Prenatal diagnosis

Clinical testing

- **Duplication/deletion analysis**
  - **Southern blot**

    Kearns-Sayre syndrome. Deletions can vary in size and abundance among affected individuals, but deleted mtDNA of a given length is present in each individual. Approximately 90% of individuals with KSS have a large-scale (i.e., 2-10 kb) mtDNA deletion.

    Note: (1) Deletions are usually present in all tissues of individuals with KSS, and can be looked for in blood leukocytes. However, the occurrence of "heteroplasmy" in disorders of mtDNA can result in varying tissue distribution of "deleted" mtDNA. Since mutant mtDNA may be undetectable in blood cells, muscle biopsy may be necessary. (2) Large-scale duplications of mtDNA coexist with deletions in some individuals with KSS [Poulton et al 1989].

    Pearson syndrome. Mitochondrial DNA deletions are usually more abundant in blood than in other tissues. The diagnosis of Pearson syndrome is reliably made by Southern blot analysis of leukocytes.

    Progressive external ophthalmoplegia (PEO). Mitochondrial DNA deletions are confined to skeletal muscle. The molecular diagnosis of PEO requires Southern blot analysis of a muscle biopsy [Moraes et al 1989].
  - **Long PCR analysis.** Long PCR analysis detects deletions throughout the mtDNA; however, this method has high sensitivity and low specificity. Because mtDNA deletions accumulate normally with age, detection of the common deletion or of multiple deletions by PCR may lead to misdiagnosis. As a result, Southern blot analysis is the preferred method for diagnosis.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Mitochondrial DNA Deletion Syndromes

Test Method	Mutations Detected	Mutation Detection Frequency [1, 2]		Test Availability
		Kearns-Sayre Syndrome	PEO	
Duplication/deletion analysis [3]	Mitochondrial DNA deletions	90%	50%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method
2. For KSS and Pearson syndrome, the detection rate is not 100% because rare individuals have syndromes that mimic KSS but are caused by other mtDNA mutations. For PEO, however, numerous mutations in either mtDNA or nuclear genes also cause PEO often associated with other manifestations.
3. Long PCR analysis detects deletions throughout the mtDNA; however, this method has high sensitivity and low specificity. Because mtDNA deletions accumulate normally with age, detection of the common deletion or of multiple deletions by PCR may lead to misdiagnosis. As a result, Southern blot analysis is the preferred method for diagnosis.

Testing Strategy

The clinical diagnosis has to be confirmed by molecular studies documenting rearrangements (usually deletions, but rarely duplications, and often the two together) of mtDNA in leukocytes or muscle.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with single deletions of mtDNA. See Mitochondrial Disorders Overview.

Clinical Description

Natural History

Kearns-Sayre syndrome. KSS is a multisystem disorder affecting predominantly the central nervous system, skeletal muscle, and heart. Onset is usually in childhood, with ptosis, ophthalmoplegia, or both. Exercise intolerance and impaired night vision may be early symptoms. Dysphagia caused by incomplete opening of the upper esophageal sphincter (cricopharyngeal achalasia) is common [Kornblum et al 2001]. The disease usually progresses to death in young adulthood.

Central nervous system involvement is manifest by cerebellar ataxia, impaired intellect (mental retardation, dementia, or both), and sensorineural hearing loss. Compared to other mitochondrial encephalomyopathies (e.g., MELAS, MERRF, and NARP), KSS is notable for the extreme rarity of epilepsy. Strokes are also rare. In two individuals, strokes were attributed to cardiac emboli [Kosinski et al 1995, Provenzale & VanLandingham 1996].

Muscle involvement is manifest by PEO, ptosis, oropharyngeal dysfunction, exercise intolerance, and proximal more than distal limb muscle weakness. The defect of extraocular movement is usually symmetric but may cause blurred or double vision.

Heart involvement is characterized by conduction block, which can lead to complete heart block if a pacemaker is not placed in a timely fashion. Cardiomyopathy, less common than cardiac conduction block, has been reported in two individuals [Tranchant et al 1993, personal observation].

Endocrinopathies are common in KSS and include diabetes mellitus, hypoparathyroidism, irregular menses, and growth hormone deficiency. The diabetes mellitus is caused by insufficient insulin secretion rather than a defect of insulin receptor [Piccolo et al 1989]. Short stature may be the result of growth hormone deficiency.

Renal tubular acidosis can be part of KSS and in some cases is the presenting feature.

The **pigmentary retinopathy** of KSS affects low-light vision more prominently than visual acuity; hence, affected individuals complain of difficulty with night vision. Peripheral vision may be compromised by ptosis. Vision generally deteriorates insidiously; therefore, the age at onset is often difficult to discern (see Table 2).

Table 2. Signs and Symptoms in 86 Individuals with KSS

Sign or Symptom	Present/Evaluated	Percentage
Onset <20 yrs	86/86	100
Pigmentary retinopathy	86/86	100
PEO	86/86	100
Cerebellar syndrome	53/63	84
Limb weakness	61/65	94
Sensorineural hearing loss	33/34	97
Impaired intellect	25/29	86
Diabetes mellitus	11/86	13
Seizures	2/86	2

Pearson syndrome. Pearson syndrome is often fatal in infancy. The few individuals with Pearson syndrome who survive beyond infancy develop the symptoms and signs of KSS [Larsson et al 1990, McShane et al 1991].

Progressive external ophthalmoplegia. PEO is characterized by drooping of the eyelids (ptosis), paralysis of the extraocular muscles (ophthalmoplegia), and variably severe proximal limb weakness. The disorder is relatively benign and compatible with a normal lifespan.

Genotype-Phenotype Correlations

No correlation exists between size or location of the mtDNA deletion and phenotype.

For all mtDNA mutations, clinical expressivity depends on the three following factors:

- The relative abundance of mutant mtDNA **(heteroplasmy)**
- The tissue distribution of the mutant mtDNAs
- The vulnerability of each tissue to impaired oxidative metabolism **(threshold effect)**

The tissue vulnerability threshold probably does not vary substantially among affected individuals, but variable mutational load and tissue distribution may account for the spectrum of clinical findings in individuals with KSS.

The fact that mtDNA deletions are present in all tissues in individuals with KSS, are predominantly present in hematopoietic cells of individuals with Pearson syndrome, and are confined to skeletal muscle in PEO explains the different clinical phenotypes. The gradual decrease in mtDNA deletions in rapidly dividing blood cells and their gradual increase in post-mitotic tissues is an example of **mitotic segregation** and explains how infants with Pearson syndrome may develop KSS later in life.

Penetrance

In mtDNA-related disorders, penetrance is a function of the mutation load. As a general rule, heteroplasmic levels above 80-90% cause mitochondrial dysfunction and clinical symptoms.

Nomenclature

The general terms for the neuromuscular disorders include progressive external ophthalmoplegia (PEO) and chronic progressive external ophthalmoplegia (CPEO).

The multisystemic form is called Kearns-Sayre syndrome (KSS); in the past, KSS was also referred to as "ophthalmoplegia-plus," a term now used to describe individuals who have more than isolated myopathy but do not fulfill the canonical criteria for KSS.

For Pearson syndrome, the term "Pearson marrow pancreas syndrome" is a synonym; the term "sideroblastic anemia and exocrine pancreatic dysfunction" is not currently used.

Prevalence

No prevalence data exist for KSS. See Mitochondrial Disorders Overview for general prevalence.

Differential Diagnosis

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

Ataxia. See Hereditary Ataxia Overview.

Sensorineural hearing loss. See Hereditary Hearing Loss and Deafness Overview.

Pigmentary retinopathy. See Retinitis Pigmentosa Overview.

Sensorineural hearing loss and retinitis pigmentosa. See Usher Syndrome Type 1 and Usher Syndrome Type 2.

Progressive external ophthalmoplegia. KSS and PEO must be differentiated from other disorders associated with ophthalmoplegia. These include (with distinguishing features):

- Myasthenia gravis (fluctuating weakness and diplopia)
- Oculopharyngeal muscular dystrophy (late onset, severe dysphagia, autosomal dominant inheritance)
- Myotonic dystrophy type 1 (myotonia, autosomal dominant inheritance)
- Mendelian PEOs associated with multiple deletions of mtDNA caused by mutations in:
  - *SLC25A4*, encoding ANT1
  - *PEO1*, encoding twinkle
  - *POLG1*, encoding the catalytic subunit of mtDNA polymerase
  - *ECGF1*, encoding thymidine phosphorylase (autosomal dominant or recessive inheritance, affective disorders, and gastrointestinal dysmotility) (see MNGIE Syndrome)
- Maternally inherited PEOs caused by various mtDNA point mutations (maternal inheritance) [Hirano & DiMauro 2001, Lamantea et al 2002, Agostino et al 2003, Filosto et al 2003]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with a mitochondrial DNA deletion syndrome:

- Complete neurologic, cardiologic, ophthalmologic, and endocrinologic evaluations for KSS and PEO
- Complete hematologic and gastroenterologic evaluations for Pearson syndrome

Treatment of Manifestations

- Placement of cardiac pacemaker in individuals with cardiac conduction block to reduce the risk of sudden death
- Placement of eyelid slings for severe ptosis
- Cochlear implants and hearing aids for neurosensory hearing loss
- Hormone replacement for endocrinopathies
- Dilation of the upper esophageal sphincter to alleviate cricopharyngeal achalasia
- Folinic acid supplementation in individuals with KSS with low CSF folic acid
- Replacement of pancreatic enzymes in Pearson syndrome
- Administration of coenzyme Q10 (50-200 mg 3x/day) and L-carnitine (1,000 mg 3x/day)
- Physical and occupational therapy
- Treatment of depression

Prevention of Secondary Complications

- Antioxidants may ameliorate damage from reactive oxygen species (ROS)
- Percutaneous endoscopic gastrostomy (PEG) may improve nutritional intake and prevent aspiration pneumonia in individuals with severe dysphagia.

Surveillance

- EKG and echocardiogram every six to 12 months to monitor cardiac conduction and contractility
- Yearly audiometry and endocrinologic evaluation

Agents/Circumstances to Avoid

- Drugs potentially toxic to mitochondria, including chloramphenicol, aminoglycosides, linezolide, valproic acid, nucleoside reverse transcriptase inhibitors.
- Dichloroacetate (DCA) as a lactate-lowering agent, as DCA has been proven to cause peripheral neuropathy [Kaufmann et al 2006]

Testing of Relatives at Risk

Symptomatic maternal relatives should be screened for the specific mtDNA deletion.

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

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

Mitochondrial DNA deletion syndromes are caused by deletion of mtDNA and, when inherited, are transmitted by maternal inheritance.

Risk to Family Members

Parents of a proband

- The father of a proband is not at risk of having the disease-causing mtDNA mutation.
- The mother of a proband with a mtDNA deletion syndrome is usually unaffected and does not have mtDNA deletions in her tissues.
- The mtDNA deletion is usually *de novo* in the proband, occurring either in the mother's oocyte or during embryogenesis.

Sibs of a proband

- The risk to the sibs of a proband is usually extremely low.
- If the mother and one child are affected, the risk to other children is very low: thus far, maternal transmission to more than one child has not been reported.

Offspring of a proband

- Affected women have a small but finite chance of having an affected child, calculated at 1 in 24 births [Chinnery et al 2004].
- Offspring of males with a mtDNA mutation are not at risk.

Other family members of a proband. The risk to other family members of being affected or of having a mtDNA deletion is extremely low.

Related Genetic Counseling Issues

Family planning. The phenotype of an individual with a mtDNA deletion results from a combination of factors including the severity of the mutation, the percentage of mutant mitochondria, and the organs and tissues in which they are found. Deletions of mtDNA usually

affect one single member of a family. However, in two of the three inherited cases, the mother had a different phenotype (PEO) from the child (Pearson syndrome).

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

Although prenatal testing is available on a clinical basis, accurate interpretation of prenatal diagnostic results of a mtDNA mutation is extremely problematic. In women with KSS, detection of the mtDNA deletion in amniocytes or chorionic villi may be possible, but in cases of progressive external ophthalmoplegia (PEO) the deletion is confined to skeletal muscle and is thus not detectable by prenatal diagnosis. In addition, the finding of the mtDNA mutation in one tissue may not be a reflection of its presence in other tissues. Because of mitotic segregation, the mtDNA mutational load in amniocytes and chorionic villi is unlikely to correspond to that of other fetal or adult tissues. Prediction of phenotype, age of onset, severity, or rate of progression is not possible.

Molecular Genetics

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

Table A. OMIM Entries for Mitochondrial DNA Deletion Syndromes

157640	PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA WITH MITOCHONDRIAL DNA DELETIONS, AUTOSOMAL DOMINANT, 1
530000	KEARNS-SAYRE SYNDROME; KSS
557000	PEARSON MARROW-PANCREAS SYNDROME

Molecular Genetic Pathogenesis

Mitochondrial DNA deletion syndromes are almost never inherited, suggesting that these disorders are caused by *de novo* mtDNA deletions that occur in the mother's oocytes during germline development or in the embryo during embryogenesis. Chen et al (1995) showed that the "common deletion" accounted for 0.1% of the approximately 150,000 mtDNAs in a human oocyte. A "bottleneck" between oocyte and embryo allows only a minority of maternal mtDNAs to populate the fetus. On rare occasions, a "deleted" mtDNA may slip through. From the blastocyst, deleted mtDNAs can enter all three germ layers and cause KSS, segregate predominantly to the hematopoietic lineage and cause Pearson syndrome, or segregate to muscle and cause PEO [DiMauro & Schon 2003].

The origin of mtDNA deletions is uncertain. However, it has been noted that deletions fall into two classes [Mita et al 1990]: class I mutations are flanked by perfect direct repeats; class II mutations are not flanked by any unique elements. Homologous recombination or slipped mispairing (i.e., unequal crossing over) may explain the origin of class I deletions, but the genesis of class II deletions remains unknown. The fact that a mtDNA deletion of a given length is found in a given individual implies that the population of deleted mtDNAs is a clonal expansion of a single mutation event that occurred early in oogenesis or in embryogenesis [Schon 2003]. The hypothesis of clonality implies that a single rearranged molecule present in the oocyte or the embryo multiplies wildly to form the trillions of deleted mtDNAs in the

affected individual. How the selective amplification of deleted mtDNAs occurs is currently unknown, but the bottleneck concept described above may provide an answer.

Normal allelic variants: See Mitochondrial Disorders Overview.

Pathologic allelic variants: Deletions can vary in size and abundance among affected individuals, but deleted mtDNA of a given length is present in each individual. Approximately 90% of individuals with KSS have a large-scale (i.e., 2-10 kb) mtDNA deletion. The "common" 4977-bp deletion is present in about one-third of affected individuals.

Normal gene product: See Mitochondrial Disorders Overview.

Abnormal gene product: The similarly deleterious effects of different mtDNA deletions can be explained by the fact that even the smallest mtDNA deletion encompasses several tRNA genes; thus, "deleted" mtDNAs are transcribed into RNA in the usual way, but the processed transcript encoding polypeptides is not translated because the deletions remove essential tRNAs needed for protein synthesis [Schon 2003].

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.

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.

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Chapter Notes

Revision History

- 19 April 2007 (sdm) Revision: prenatal testing available on a clinical basis
- 8 February 2006 (me) Comprehensive update posted to live Web site
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