GENEReviews

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Congenital Myasthenic Syndromes

[*Congenital Myasthenia. Includes: CHAT-Related Congenital Myasthenic Syndrome, CHRNA1-Related Congenital Myasthenic Syndrome, CHRNB1-Related Congenital Myasthenic Syndrome, CHRND-Related Congenital Myasthenic Syndrome, CHRNE-Related Congenital Myasthenic Syndrome, COLQ-Related Congenital Myasthenic Syndrome, MUSK-Related Congenital Myasthenic Syndrome, RAPSN-Related Congenital Myasthenic Syndrome, SCN4A-Related Congenital Myasthenic Syndrome*]

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Summary

Disease characteristics. Congenital myasthenic syndromes (designated as CMS throughout this entry) are characterized by fatigable weakness involving ocular, bulbar, and limb muscles with onset at or shortly after birth or in early childhood; rarely, symptoms may not manifest until later in childhood. Severity and course of disease are highly variable, ranging from minor symptoms to progressive disabling weakness. In some types of CMS, myasthenic symptoms may be mild, but sudden severe exacerbations of weakness or even sudden episodes of respiratory insufficiency may occur, precipitated by fever, infections, or excitement. If symptoms start in the neonatal period, the major findings include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and facial, bulbar, and generalized weakness. Arthrogryposis may be present and respiratory insufficiency with sudden apnea and cyanosis may occur. Individuals with onset later in childhood show abnormal muscle fatigability with difficulty in running or climbing stairs. Motor milestones may be delayed. Affected individuals present with fluctuating eyelid ptosis and fixed or fluctuating extraocular muscle weakness. CMS is limited to weakness of the skeletal muscles: cardiac and smooth muscle are not involved.

Diagnosis/testing. The diagnosis of CMS is based on clinical findings, a decremental EMG response of the compound muscle action potential (CMAP) on low-frequency (2-3 Hz) stimulation, negative tests for anti-acetylcholine receptor (AChR) and anti-MuSK antibodies in the serum, and lack of improvement of clinical symptoms with immunosuppressive therapy. Several genes encoding proteins expressed at the neuromuscular junction are currently known to be associated with CMS. These include the genes encoding different subunits of the acetylcholine receptor *(CHRNE*: εAChR-subunit; *CHRNA1*: αAChR-subunit; *CHRNB1*: βAChR-subunit; *CHRND*: δAChR-subunit); the gene encoding the collagenic tail subunit of the acetylcholinesterase *(COLQ)*; the gene of the choline acetyltransferase *(CHAT)*; and the gene encoding rapsyn *(RAPSN)*. Sequence analysis is clinically available for *CHRNE* and *CHRNA1*. Mutation scanning is available for *RAPSN*, *CHAT*, *COLQ*, *CHRNB1*, and *CHRND*. Targeted mutation analysis is available for *RAPSN* mutation p.N88K, *CHAT* mutation

p.I305T, and *CHRNA1* mutation p.G153S. Molecular genetic testing of the remaining genes is available on a research basis only.

Management. Most individuals with CMS benefit from AChE inhibitors and/or the potassium channel blocker 3,4-diaminopyridine (3,4-DAP), although caution must be used in giving 3,4-DAP to young children and individuals with fast-channel syndromes. Some individuals with SCCMS are treated with quinidine, which has some major side effects and may be detrimental in individuals with AChR deficiency. Fluoxetine is reported to be beneficial for the slow-channel syndrome. Ephedrine has resulted in small improvements, mainly in swallowing, in a few individuals. Prophylactic anticholinesterase therapy is used to prevent sudden respiratory insufficiency or apneic attacks provoked by fever or infections in individuals with underlying genetic defects in *CHAT* or *RAPSN*; parents of infants need to install apnea monitors in their homes and be trained in CPR.

Genetic counseling. Congenital myasthenic syndromes are inherited in an autosomal recessive, or, less frequently, autosomal dominant manner. In autosomal recessive CMS (AR-CMS), the parents of an affected child are obligate heterozygotes and therefore carry one mutant allele. Heterozygotes (carriers) are asymptomatic. 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. In autosomal dominant CMS (AD-CMS), some individuals have an affected parent while others have a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with AD-CMS has a 50% chance of inheriting the mutation. Prenatal testing is available for CMS caused by mutations in *CHAT*, *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*, *COLQ*, or *RAPSN*. Prenatal testing for other genes may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

The clinical diagnosis of congenital myasthenic syndromes (CMS) is based on:

- A history of fatigable weakness involving ocular, bulbar, and limb muscles
- Onset at or shortly after birth or in early childhood. Onset post-childhood has been observed, but is rare [Burke et al 2003, Beeson et al 2005].
- A decremental EMG response of the compound muscle action potential (CMAP) on low-frequency (2-3 Hz) stimulation
- Negative tests for anti-AChR and anti-MuSK antibodies in the serum. A negative test for anti-AChR antibodies in the serum can help distinguish CMS from myasthenia gravis (MG), but does not exclude seronegative types of MG or MG with anti-MuSK antibodies [Hoch et al 2001]. One must be cautious of the rare instance in which autoimmune MG develops in individuals with CMS [Croxen, Vincent et al 2002].
- Lack of improvement of clinical symptoms with immunosuppressive therapy
- A family history consistent with either autosomal recessive or autosomal dominant inheritance

Testing

Laboratory testing. Serum creatine kinase (CK) concentration may be normal or slightly elevated.

Electrophysiologic testing

- Generally, individuals should be tested for a decremental EMG response of the CMAP on low-frequency (2-3 Hz) stimulation.
- In some cases, 2-3 Hz stimulation elicits no decremental response from rested non-weak muscle, but elicits a significant decremental response after 5-10 min stimulation at 10 Hz.
- If the amplitude of the CMAP is normal in two distal and two proximal muscles, facial muscles should be tested.
- Alternatively or in addition, a single-fiber EMG is a good determinant of a neuromuscular transmission defect.
- A single nerve stimulus may elicit a repetitive CMAP in individuals with endplate acetylcholinesterase deficiency or slow-channel syndrome, or in those taking high doses of AChE inhibitors.

Morphologic studies. Conventional muscle biopsy and routine histochemical studies in individuals with CMS generally show no major abnormalities except for a type I fiber predominance and occasionally minor myopathic changes. More detailed studies including estimation of acetylcholine receptors (AChRs) per endplate, light and electron microscopic analysis of endplate morphology, and in vitro electrophysiologic studies of endplate function can be performed on an intercostal or motor point muscle biopsy [Engel et al 1994]. The studies allow a more precise classification by pointing to a defect in an endplate-associated gene or protein.

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. Several genes encoding different proteins expressed at the neuromuscular junction are currently known to be associated with CMS [Engel et al 2003, Hantai et al 2004, Ohno & Engel 2004a, Beeson et al 2005, Engel & Sine 2005]. These include the following (see also Table 2):

- The genes encoding different subunits of the acetylcholine receptor:
  - *CHRNE*: εAChR-subunit
  - *CHRNA1*: αAChR-subunit
  - *CHRNB1*: βAChR-subunit
  - *CHRND*: δAChR-subunit
- The gene encoding the collagenic tail subunit of the acetylcholinesterase: *COLQ*
- The gene of the choline acetyltransferase: *CHAT*
- The gene encoding rapsyn: *RAPSN*
- The gene encoding the voltage-gated sodium channel of skeletal muscle ($Na_V1.4$): *SCN4A*
- The gene encoding the muscle-specific receptor tyrosine kinase: *MUSK*

Other loci. To date, no other loci are known to be associated with CMS; however, families with CMS not linked to any of the known candidate genes have been identified. Further genetic studies may reveal new loci or candidate genes underlying CMS [Engel & Sine 2005].

Molecular genetic testing: Clinical use

- Diagnostic testing
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis**
  - *CHRNA1* (mutation p.G153S)
  - *CHAT* (mutation p.I305T)
  - *RAPSN* (mutation p.N88K in exon 2). Affected individuals of European origin, especially those with respiratory failure, have the N88K mutation on at least one allele; about 50% are homozygous for N88K.
- **Sequence analysis**
  - ***CHRNE*.** The mutation ε1267delG in exon 12 accounts for up to 50% of individuals of European Roma and/or southeastern European origin with CMS caused by a founder effect [Abicht et al 1999, Karcagi et al 2001].

    Testing for the *CHRNE* mutation 1293insG is promising in individuals with CMS originating from the Maghreb (especially Algeria and Tunisia), where the mutation accounts for up to 20% of cases attributable to a founder effect [Beeson et al 2005].

    Sequence analysis of *CHRNE* may be used to detect rare "private" mutations in southeastern European or western European individuals in whom mutation analysis does not detect the frequent mutations ε1267delG and *RAPSN* N88K, respectively.
  - ***CHRNA1***
- **Mutation scanning**
  - *CHRNB1*
  - *CHRND*
  - *COLQ*
  - *CHAT*
  - *RAPSN*. Other mutations in *RAPSN* are dispersed throughout the translated region. In case of heterozygosity for N88K, the entire gene including the promoter should be sequenced to detect a second heteroallelic mutation. In the promoter, mutations have been identified in the E-box element.

    One E-box mutation, -38A>G, observed in the homozygous state, arose from a common founder in Near-Eastern Jews with marked jaw and other facial malformations [Ohno et al 2003].

    One E-box mutation, -27C>G, was heterozygous with the N88K mutation [Ohno et al 2003].

Molecular genetic testing: Research

- **Linkage analysis.** Linkage analysis may be used in families in which direct DNA testing has not identified both CMS mutations.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Congenital Myasthenic Syndromes

Population	Test Method	Mutations Detected	Mutation Detection Rate [1]	Proportion of CMS attributed to mutations in this gene [2]	Test Availability
Roma/ southeastern European individuals	Sequence analysis/ mutation scanning	ε1267delG (founder mutation) in *CHRNE*	>25%	>50%	Clinical Testing
The Maghreb (especially Algeria and Tunisia)		1293insG mutation in *CHRNE*	>10%	20%	
Affected individuals of diverse origins (mainly caucasians)		Sequence variants in *CHRNE*	30%	60%	
		Sequence variants in *CHRNA1*	<0.5%	<1%	Clinical Testing
		Sequence variants in *CHRNB1*	<0.5%	<1%	Clinical Testing
		Sequence variants in *CHRND*	<0.5%	<1%	Clinical Testing
		Sequence variants in *COLQ*	<7.5%	10%-15%	Clinical Testing
		Sequence variants in *CHAT*	<3%	5%	Clinical Testing
		Sequence variants in *RAPSN*	<10%	20%	Clinical Testing
		Sequence variants in *SCN4A*	<0.5%	<1%	Research only
		Sequence variants in *MUSK*	<0.5%	<1%	

1. Based on individuals with CMS investigated at the authors' laboratory, the estimated mutation detection rate in CM is at least 50% if all known CMS genes are analyzed. Because of the presence of founder mutations, the overall detection rates in specific populations (Roma, Maghreb ethnic origin) may be even higher.
2. Estimated percentage based on individuals with CMS investigated at the authors' laboratory and on published data [Beeson et al 2005, Engel & Sine 2005]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

Figure 1 provides a genetic testing algorithm to help the clinician pinpoint the most likely causative gene in individuals with CMS based mainly on family size, ethnic origin, inheritance pattern, and phenotypic findings.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *CHRNE,CHRNA1,CHRNB1,CHRND,COLQ,CHAT,RAPSN,* and *MUSK.*

Gain-of-function mutations of the skeletal muscle sodium channel gene *SCN4A* have been identified in a variety of disorders of muscle membrane excitability: potassium-aggravated

myotonia, paramyotonia congenita, and hyperkalemic periodic paralysis (for review, see Cannon 2000).

Clinical Description

Natural History

In general, the first myasthenic symptoms occur early in life, usually in the first two years. Rarely, onset is in the second to third decade of life [Milone et al 1999; Croxen, Hatton et al 2002; Burke et al 2003]. Severity and course of disease are highly variable, ranging from minor symptoms to progressive disabling weakness. In some types of CMS, myasthenic symptoms may be mild, but sudden severe exacerbations of weakness or even sudden episodes of respiratory insufficiency may occur. They may be precipitated by fever, infections, or excitement and are most frequently seen in individuals with CMS with episodic apnea (CMS-EA) or endplate rapsyn deficiency (EP rapsyn deficiency) [Ohno et al 2001, Byring et al 2002, Ohno et al 2002].

Some individuals present with myasthenic symptoms at birth. Neonates with arthrogryposis multiplex congenita resulting from a lack of fetal movement in utero have been reported to have CMS. Arthrogryposis seems to be particularly common in individuals with neonatal onset of symptoms and truncating mutations of the rapsyn gene [Brownlow et al 2001, Burke et al 2003, Beeson et al 2005]. If symptoms start in the neonatal period, the major findings include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and facial, bulbar, and generalized weakness. Respiratory insufficiency with sudden apnea and cyanosis may occur at birth or may be provoked by fever or infection later in childhood.

Individuals with onset later in childhood show abnormal muscle fatigability, with difficulty in running or climbing stairs. Motor milestones may be delayed. Affected individuals present with fluctuating eyelid ptosis and fixed or fluctuating extraocular muscle weakness. Ptosis may involve one or both eyelids. In addition, facial and bulbar weakness with nasal speech and difficulties in coughing and swallowing may be present.

Spinal deformity or muscle atrophy may occur.

In some individuals, a high-arched palate and other distinctive facial features have been reported.

CMS is limited to weakness of the skeletal muscles. Cardiac and smooth muscle are not involved. Cognitive skills, coordination, sensation, and tendon reflexes are normal.

CMS subtypes are recognized based on molecular genetic studies in research laboratories (Table 2):

- CMS with episodic apnea (CMS-EA)
- Endplate acetylcholinesterase deficiency (EP AChE deficiency)
- Acetylcholine receptor deficiency (AChR deficiency)
- Slow-channel syndrome (SCCMS)
- Fast-channel syndrome (FCCMS)
- Endplate rapsyn deficiency (EP rapsyn deficiency)

Table 2. Genotype-Phenotype Correlation in CMS

Disease-Causing Genes	Type of CMS	Clinical	Response to AChE Inhibitors [1]
AChR subunit genes: *CHRNE*, *CHRNA1*, *CHRNB1*, *CHRND*	Acetylcholine receptor deficiency (AChR deficiency)	Early onset Varies from mild to severe Ptosis, EOP [2]; bulbar, arm, leg weakness	Improve
	Slow-channel syndrome (SCCMS)	Selective severe neck, wrist, finger extensor weakness Onset varies from childhood to adult Varies from mild to severe Progressive ventilatory insufficiency may require assisted ventilation.	Often deterioration
	Fast-channel syndrome	Varies from mild to severe Phenotype is highly variable.	Improve
RAPSN	Endplate rapsyn deficiency (EP rapsyn deficiency)	Rapsyn-EO (early onset) Hypotonia, respiratory failure at birth Episodic apnea Arthrogryposis Varies from mild to severe Rapsyn-LO (late onset) Limb weakness in adolescence or adulthood resembling seronegative myasthenia gravis Other [3]	Improve
CHAT	Congenital myasthenic syndrome with episodic apnea (CMS-EA)	Hypotonia, respiratory failure at birth Episodic apnea Improvement with age	Improve
COLQ	Endplate acetylcholinesterase deficiency (EP AChE deficiency)	Often severe Some with C-terminal missense mutations present later and have milder clinical course. Ophthalomoparesis General muscle weakness/severe involvement of axial muscles Slow pupillary light response	Deterioration or no response

From Ohno et al 2001, Byring et al 2002, Ohno et al 2002, Burke et al 2003, Beeson et al 2005]. Because of the many private mutations and the limited number of genotype-phenotype correlations, the clinical spectrum may be broader or even differ from the symptoms listed.

1. Response to acetylcholinesterase inhibitors is assessed using intraveneous injection of edrophonium (Tensilon®, a fast-acting acetylcholinesterase inhibitor). An initial dose of 2 mg is injected over 15 seconds, followed by additional doses of 3 mg and 5 mg at intervals of 60 seconds, if necessary. Maximum improvement occurs within 30 seconds of the injection and persists for minutes. An objective endpoint (e.g., improvement in ptosis, extraocular muscle weakness, tongue weakness, decremental EMG response) needs to be established prior to the injection and then carefully followed.

2. EOP = external ophthalmoplegia

3. A recessive E-box mutation in the *RAPSN* promotor region results in benign CMS with distinct facial malformation [Ohno et al 2003].

Other types of CMS have been reported in the literature in a few kinships [Bady et al 1987, Walls et al 1993, Banwell et al 1999, Rodolico et al 2002, Beeson et al 2005]. Some have been thoroughly characterized by morphologic and in vitro electrophysiologic studies pointing toward a presumed lesion, but others are not yet completely classified. In these CMS types, the underlying genetic defect has not yet been identified.

Genotype-Phenotype Correlations

Some clinical clues point to specific genetic defects [Engel 2001, Ohno et al 2001, Byring et al 2002, Engel & Ohno 2002, Ohno et al 2002, Burke et al 2004, Beeson et al 2005]. See Table 2.

Penetrance

In general, reported CMS mutations have complete penetrance.

One case of reduced penetrance has been reported for a slow-channel syndrome [Croxen, Hatton et al 2002].

Late onset of clinical symptoms in individuals with the *RAPSN* mutation N88K may resemble incomplete penetrance in a family.

Anticipation

Anticipation has not been described.

Nomenclature

An outdated and misleading term is familial infantile myasthenia (FIM) [Deymeer et al 1999].

Prevalence

At least 600 independent kinships with identified mutations have been documented worldwide.

The population of the southeastern European Roma may be at higher risk for CMS because of an increased carrier rate (>4%) for a specific recessive mutation *(CHRNE* 1267delG) of the εAChR subunit gene [Morar et al 2004]. Such may also be the case for individuals from the Maghreb (especially Algeria and Tunisia) because of another founder mutation in the *CHRNE* gene *(CHRNE* 1293insG) [Beeson et al 2005].

RAPSN mutations are likely one of the most common causes for CMS in individuals of Indo-European ethnic origin [Müller et al 2003, Richard et al 2003].

The prevalence of CMS is lower than that of myasthenia gravis (25:1,000,000-125:1,000,000). The prevalence of CMS is estimated to be one-tenth that of myasthenia gravis, although it may be higher.

Differential Diagnosis

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

Myasthenia gravis. The clinical picture of CMS is similar to that of myasthenia gravis (MG), in which individuals have a history of fatigable weakness involving ocular, bulbar, and limb muscles; however, the myasthenic symptoms of CMS usually start at or shortly after birth rather than in adulthood, as is usual for MG. Seronegative autoimmune MG, has been reported in children as young as two years of age. Therefore, MG may be difficult to differentiate from CMS in later childhood or adulthood. Furthermore, immunosuppressive therapy does not lead to an improvement of clinical symptoms in CMS, whereas it does in MG.

Transient neonatal myasthenia gravis. Autoimmune MG can be passed across the placenta from mother to fetus and so can affect offspring at birth.

Other disorders partially resembling CMS in childhood include spinal muscular atrophy (genetic testing: *SMN1* gene deletions; mutations in *SMARD*), congenital muscular dystrophies (dystrophic changes in muscle biopsy), congenital myopathies such as X-linked myotubular myopathy, nemaline myopathy, and multiminicore myopathy (all have characteristic findings in muscle biopsy), infantile myotonic dystrophy type 1 (genetic testing: expansion of CTG repeats in the 3' UTR of the *DMPK* gene), mitochondrial myopathies (genetic testing, muscle biopsy, biochemical diagnosis of mitochondrial respiratory chain defects), brain-stem anomalies (brain imaging studies), Mobius syndrome (brain imaging, electrophysiological studies), or infantile botulism (constipation as first symptom, sudden and rapidly progressive symptoms).

In adulthood, motor neuron disease such as spinal and bulbar muscular atrophy (SBMA, Kennedy disease; genetic testing: CAG repeat expansion in the first exon of the androgen receptor (AR) gene), limb girdle muscular dystrophy (alterations in muscle biopsy), facioscapulohumeral dystrophy (genetic testing: 4q35 deletion), mitochondrial myopathy and chronic progressive external opthalmoplegia (CPEO) (genetic testing, muscle biopsy), autosomal dominant progressive external opthalmoplegia (ADPEO; isolated ocular symptoms in two generations, eventually mutations in *ANT1,TWINKLE,* or *POLG)*, and chronic fatigue syndrome (e.g., normal findings in electrophysiology) should be considered.

Management

Treatment of Manifestations

- The majority of individuals with CMS benefit from AChE inhibitors, although some myasthenic symptoms may remain refractory to treatment even in otherwise responsive individuals. Certain CMS subtypes, such as EP AChE deficiency and the SCCMS, are refractory to or deteriorate with AChE inhibitors [Engel et al 1994] (see Table 2).
- Alternatively or in addition, the potassium channel blocker 3,4-diaminopyridine (3,4-DAP) may be used [Palace et al 1991, Anlar et al 1996, Banwell et al 2004, Beeson et al 2005]. This drug increases the release of ACh and prolongs the presynaptic action potential. Of note, two children who had fast-channel mutations died when started on 3,4-DAP [Beeson et al 2005]. A relation to 3,4-DAP has not been proven, but clinicians must be cautious when using 3,4-DAP in young children and in individuals with fast-channel disease.
- Some individuals with genetically defined SCCMS have been successfully treated with quinidine, a long-lived open-channel blocker of AChR [Harper & Engel 1998]. This treatment in turn may be detrimental in individuals with AChR deficiency. Quinidine has some major side effects including torsades de pointes, a potentially life-threatening arrhythmia, hypotension, cinchonism (or quininism), and hypersensitivity reactions. In individuals with CMS, adverse effects, such as exacerbation of weakness and development of respiratory failure, may occur.
- Recently, the therapeutic benefit of fluoxetine in the slow-channel syndrome has been shown [Harper et al 2003].
- Ephedrine treatment (alternatively or in addition to mestinon) resulted in a small overall improvement in five individuals (unblinded; three with CHRNE null mutations, one with slow-channel syndrome, and two unknown CMS). Swallowing improved dramatically [Beeson et al 2005].

Prevention of Primary Manifestations

Sudden respiratory insufficiency or apneic attacks provoked by fever or infections are common in individuals with underlying genetic defects in CHAT or RAPSN, even if the myasthenic symptoms are mild between crises. These individuals should receive prophylactic anticholinesterase therapy. In infants, an apnea monitor should be installed at home and the parents should be trained in cardiopulmonary resuscitation (CPR).

Agents/Circumstances to Avoid

A number of drugs are known to affect neuromuscular transmission and therefore exacerbate symptoms of myasthenia gravis (e.g., ciprofloxacin, chloroquine, procaine, lithium, phenytoin, beta-blockers, procainamide, and quinidine). These drugs are not absolutely contraindicated and may be used with caution in CMS.

A more complete list can be obtained online (see Neuromuscular Disease Center).

Therapies Under Investigation

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

Congenital myasthenic syndromes are inherited in an autosomal recessive, or, less frequently, autosomal dominant manner [Hantai et al 2004, Ohno & Engel 2004a, Engel & Sine 2005]. Most of the slow-channel syndromes are inherited in an autosomal dominant manner.

Risk to Family Members — Autosomal Recessive Inheritance

Parents of a proband

- The parents of a child with autosomal recessive congenital myasthenic syndrome (AR-CMS) 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 chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- The offspring of an individual with AR-CMS are obligate heterozygotes (carriers) for a disease-causing mutation.
- The risk that the offspring will inherit a second disease-causing CMS allele depends upon the carrier status of the proband's reproductive partner.
- The CMS carrier frequency in the general population is low.
- In populations with a high carrier rate and/or a high rate of consanguineous marriages, the risk to the offspring of an affected individual of being affected is increased.

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

Specific risk issues. The risk for CMS is increased in the southeastern European population and in all Roma (high carrier frequency). The same may be true in the Maghreb population (especially Algeria and Tunisia) [Beeson et al 2005].

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

Risk to Family Members — Autosomal Dominant Inheritance

Parents of a proband

- Some individuals diagnosed with autosomal dominant congenital myasthenic syndrome (AD-CMS) have an affected parent.
- A proband with AD-CMS may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is unknown.

Sibs of a proband

- The risk to the sibs of the proband depends upon the status of the parents.
- If a parent is affected, the risk is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband is unknown.

Offspring of a proband. Each child of an individual with AD-CMS has a 50% chance of inheriting the mutation.

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

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification fo carrier status, and discussion of the availability of prenatal testing is before pregnancy.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

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 or when the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for CMS caused by mutations in *CHAT*, *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*, *COLQ*, or *RAPSN* is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-

causing allele(s) of an affected family member must be identified before prenatal testing can be performed.

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

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation(s) has/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 Congenital Myasthenic Syndromes

Gene Symbol	Chromosomal Locus	Protein Name
CHAT	10q11.2	Choline O-acetyltransferase
CHRNA1	2q24-q32	Acetylcholine receptor protein subunit alpha
CHRNB1	17p12-p11	Acetylcholine receptor protein subunit beta
CHRND	2q33-q34	Acetylcholine receptor protein subunit delta
CHRNE	17p13-p12	Acetylcholine receptor protein subunit epsilon
COLQ	3p25	Acetylcholinesterase collagenic tail peptide
MUSK	9q31.3-q32	Muscle, skeletal receptor tyrosine protein kinase
RAPSN	11p11.2-p11.1	43 kDa receptor-associated protein of the synapse
SCN4A	17q23.1-q25.3	Sodium channel protein type 4 subunit alpha

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 Congenital Myasthenic Syndromes

100690	CHOLINERGIC RECEPTOR, NICOTINIC, ALPHA POLYPEPTIDE 1; CHRNA1
100710	CHOLINERGIC RECEPTOR, NICOTINIC, BETA POLYPEPTIDE 1; CHRNB1
100720	CHOLINERGIC RECEPTOR, NICOTINIC, DELTA POLYPEPTIDE; CHRND
100725	CHOLINERGIC RECEPTOR, NICOTINIC, EPSILON POLYPEPTIDE; CHRNE
118490	CHOLINE ACETYLTRANSFERASE; CHAT
601296	MUSCLE, SKELETAL, RECEPTOR TYROSINE KINASE; MUSK
601462	MYASTHENIC SYNDROME, CONGENITAL, SLOW-CHANNEL; SCCMS
601592	RECEPTOR-ASSOCIATED PROTEIN OF THE SYNAPSE, 43-KD; RAPSN
603033	COLLAGENIC TAIL OF ENDPLATE ACETYLCHOLINESTERASE; COLQ
603967	SODIUM CHANNEL, VOLTAGE-GATED, TYPE IV, ALPHA SUBUNIT; SCN4A
608931	MYASTHENIC SYNDROME, CONGENITAL, ASSOCIATED WITH ACETYLCHOLINE RECEPTOR DEFICIENCY

Table C. Genomic Databases for Congenital Myasthenic Syndromes

Gene Symbol	Locus Specific	Entrez Gene	HGMD
CHAT		1103 (MIM No. 118490)	CHAT
CHRNA1		1134 (MIM No. 100690)	CHRNA1
CHRNB1		1140 (MIM No. 100710)	CHRNB1
CHRND		1144 (MIM No. 100720)	CHRND
CHRNE		1145 (MIM No. 100725)	CHRNE
COLQ	COLQ	8292 (MIM No. 603033)	COLQ
MUSK		4593 (MIM No. 601296)	MUSK
RAPSN		5913 (MIM No. 601592)	RAPSN
SCN4A		6329 (MIM No. 603967)	SCN4A

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

Molecular Genetic Pathogenesis

The understanding of the molecular basis of the different types of CMS has been evolving since 1995. After the identification of mutations in the subunits of the nicotinic acetylcholine receptor (AChR), other genes encoding postsynaptic, presynaptic, or synaptic proteins were identified as candidate genes for CMS [Engel et al 2003, Hantai et al 2004, Ohno & Engel 2004a, Beeson et al 2005, Engel & Sine 2005]. Currently, several proteins expressed at the neuromuscular junction and involved in neuromuscular transmission have been found to be involved in CMS. CMS types have been classified according to the site of the underlying defect into presynaptic, synaptic, and postsynaptic CMS. This classification is still tentative because it is likely that additional types of CMS will be discovered.

The neuromuscular junction (NMJ). Neuromuscular transmission depends on the calcium-dependent release of acetylcholine (ACh) from the presynaptic nerve terminal and its interaction with AChRs on the postsynaptic membrane. ACh is first synthesised in the motor nerve terminal by the action of the enzyme choline acetyltransferase (ChAT), and is transported into the synaptic vesicles via a specific uptake mechanism. Following depolarization of the motor nerve terminal by the axonal action potential, calcium influx via voltage-gated calcium channels triggers events that lead to vesicle fusion and release of acetylcholine. Binding of ACh to AChR leads to the opening of the AChR ion channel resulting in depolarization of the postsynaptic membrane. If this depolarization exceeds that required to open the voltage-gated sodium channels on the postsynaptic side, an action potential is generated and propagated throughout the muscle fiber, leading to contraction of the muscle. ACh is hydrolyzed by the enzyme acetylcholinesterase (AChE), which is localized at the basal lamina of the NMJ, and the membrane potential of the presynaptic membrane is restored when voltage-gated potassium channels open.

Presynaptic CMS

Defect in acetylcholine resynthesis (CMS-EA): caused by mutations in the choline acetyltransferase gene *CHAT* (10q11.2). A presynaptic type of CMS has been linked to recessive loss-of-function mutations in *CHAT*, the gene encoding choline acetyltransferase (ChAT) [Ohno et al 2001].

Normal allelic variants: The gene *CHAT* consists of 18 exons.

Pathologic allelic variants: At least 15 different recessive mutations (missense, frameshift, and stop mutations) have been identified in 16 CMS kinships clinically characterized as CMS-EA [Ohno et al 2001, Maselli et al 2003, Schmidt et al 2003, Barisic et al 2005, OMIM 118490].

Normal gene product: ChAT catalyzes the reversible synthesis of acetylcholine from acetyl-coenzyme A and choline.

Abnormal gene product: Biochemical studies have established reduced catalytic efficiency and/or reduced expression of mutated gene products.

Synaptic CMS

Endplate acetylcholinesterase deficiency (EP AChE deficiency): caused by mutations in the gene *COLQ*. The synaptic type of CMS is caused by the absence of acetylcholinesterase (AChE) from the synaptic cleft as a consequence of mutations in the triple-stranded collagenic tail (ColQ) anchoring the enzyme to the synaptic basal lamina [Camp et al 1995, Donger et al 1998, Ohno et al 1998, Ohno et al 2000].

Normal allelic variants: The gene *COLQ* encoding the collagenic tail ColQ consists of 18 exons.

Pathologic allelic variants: All individuals with endplate EP AChE deficiency described to date have pathogenic mutations in the *COLQ* gene. To date, 25 mutations (missense, frameshift, stop, and splice site mutations) have been identified in several CMS kinships [Donger et al 1998; Ohno et al 1998; Ohno, Brengman et al 1999; Ohno et al 2000; Shapira et al 2002; Ishigaki et al 2003; Müller, Petrova et al 2004, OMIM 603034].

Normal gene product: The endplate species of AChE is a heteromeric asymmetric enzyme composed of one, two, or three homotetramers of globular catalytic subunits ($AChE_T$) attached to a triple-stranded collagenic tail (ColQ) anchoring the enzyme to the synaptic basal lamina. ColQ has an N-terminal proline-rich region attachment domain (PRAD), a collagenic central domain, and a C-terminal region enriched in charged residues and cysteines. Each ColQ strand can bind an $AChE_T$ tetramer to its PRAD, giving rise to A_4, A_8, and A_{12} species of asymmetric AChE. Two groups of charged residues in the collagen domain (heparan sulfate proteoglycan binding domains [HSPBD]) plus other residues in the C-terminal region assure that the asymmetric enzyme is inserted into the synaptic basal lamina. The C-terminal region is also required for initiating the triple helical assembly of ColQ that proceeds from a C- to an N-terminal direction in a zipper-like manner.

Abnormal gene product: Biochemical studies have established three major types of mutations:

- PRAD mutations prevent attachment of $AChE_T$ to ColQ;
- Collagen-domain mutations produce a short, single-stranded ColQ that binds a single $AChE_T$ tetramer and is insertion incompetent;
- C-terminal mutations hinder the triple helical assembly of the collagen domain, or produce an asymmetric species of AChE that is insertion incompetent, or both.

Neuromuscular transmission in absence of AChE is compromised by a desensitization and depolarization block of AChR at physiologic rates of stimulation, an endplate myopathy caused by cholinergic overactivity with a likely compensatory smallness of the nerve terminals and their encasement by Schwann cells. Endplate potentials and currents are prolonged in the absence of AChE, eliciting repetitive compound muscle action potentials.

Postsynaptic CMS

The majority of postsynaptic CMS types identified to date are caused by mutations in AChR subunit genes that either increase or decrease the response to acetylcholine. Recently, mutations in the gene encoding rapsyn have been identified as the genetic causes of another postsynaptic CMS [Engel et al 2003, Hantai et al 2004, Ohno & Engel 2004a, Engel & Sine 2005].

Mutations in acetylcholine receptor subunit genes. After binding acetylcholine, the AChR responds by an extensive change in conformation that affects all subunits and leads to the opening of an ion-conducting channel. The adult muscle AChR is composed of five homologous subunits: two αsubunits, and one each of β, δ, and ε. Each subunit has a large N-terminal extracellular domain, four transmembrane segments (M1-M4) with the M2 domain lining the cation-selective pore. Each AChR has two acetylcholine binding pockets, one at the α/ε interface and one at the α/δ interface.

CMS with kinetic abnormalities of the acetylcholine receptor (slow-channel syndromes and fast-channel syndromes): caused by mutations in the acetylcholine receptor subunit genes *CHRNA1*; *CHRNB1*; *CHRND*; *CHRNE*. Two major kinetic abnormalities of AChR, resulting in slow-channel syndromes and fast-channel syndromes, have emerged. The two kinetic syndromes are physiologic and morphologic opposites and call for different modalities of therapy.

Normal allelic variants: *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*

Pathologic allelic variants:

- **Slow-channel syndrome.** The majority of slow-channel syndromes are caused by dominant gain-of-function mutations. To date, no fewer than 18 autosomal dominant missense mutations have been described (see Ohno & Engel 2004a and Engel & Sine 2005). However, recessive mutations resulting in a slow-channel syndrome have been described, recently [Croxen, Hatton et al 2002]. Mutations have been identified in different AChR subunits and in different functional domains of the subunits. Several mutations are located in the transmembrane domains (M2 domains of α, β, δ, and εsubunits, and in the M1 domain of the α, β, and εsubunit) or in the extracellular domain of the αand εsubunit (see OMIM 601462).
- **Fast-channel syndrome.** The fast-channel CMSs are caused by recessive loss-of-function mutations. Thirteen fast-channel mutations have been identified (see Ohno & Engel 2004a and Engel & Sine 2005). The mutations are located in different functional domains of the AChR α, β, and δsubunit. Usually, the mutated allele causing the kinetic abnormality is accompanied by a null mutation in the second allele. In all cases, the kinetic mutation dominates the clinical phenotype.

Normal gene product: The five homologous subunits of the adult AChR (two αsubunits, and one each of β, δ, and ε) each have a large N terminal extracellular domain and four transmembrane segments (M1-M4); the M2 domain lines the cation-selective pore.

Abnormal gene product:

- **Slow-channel syndrome.** Patch-clamp studies of mutant AChR channels reveal prolonged activation episodes of the AChR in the presence of ACh. This results in prolonged endplate currents and potentials, exceeding the refractory period of the muscle fiber action potential. Therefore, a single nerve stimulus elicits one or more repetitive CMAPs as described in Harper & Engel 1998. During physiologic activity, the prolonged endplate potentials may undergo staircase summation producing a depolarization block. Moreover, these factors cause cationic overloading of the

junctional sarcoplasm resulting in myopathic changes with loss of AChR from degenerating junctional folds and an altered endplate geometry with widening of the synaptic space and subsynaptic alterations.

- **Fast-channel syndrome.** In this type of CMS with kinetic abnormalities of the AChR, the channel-opening events are abnormally brief and there are usually fewer activation episodes. Fast-channel mutations affect one or more of the following functions of AChR: affinity for ACh, efficiency of gating, and stabilization of channel kinetics. Endplate studies reveal normal or reduced AChR numbers. The structural integrity of the postsynaptic membrane is preserved. The common electrophysiologic features are rapidly decaying endplate currents, abnormally brief channel activation periods, and a reduced quantal response owing to the reduced probability of channel opening.

Acetylcholine receptor deficiency with or without minor kinetic abnormality: caused by mutations in the acetylcholine receptor subunit genes *CHRNA1*; *CHRNB1*; *CHRND*; *CHRNE*

Normal allelic variants: *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*

Pathologic allelic variants: The AChR subunits in individuals with CMS have numerous homozygous or, more frequently, heteroallelic recessive mutations that result in a reduced number of functional AChRs at the postsynaptic membrane. These low-expressor or null mutations have been reported in all subunits of the adult AChR. However, they are concentrated in the εsubunit and especially in its long cytoplasmic M3/M4 linker. To date, there are more than 50 εsubunit mutations reported (see Ohno & Engel 2004a and Engel & Sine 2005). Most such mutations are either nonsense, splice site, or frameshift mutations resulting in a premature termination of the translational chain. In addition, missense mutations alter residues essential for assembly (e.g., glycolsylation sites, the cystine loop) or in the signal peptide, also resulting in reduced gene expression. Some missense mutations affecting AChR gene expression also have accompanying kinetic effects. Furthermore, point mutations of a regulatory element (N-box) in the AChRε promoter region have been shown to result in reduced gene expression [Nichols et al 1999; Ohno, Anlar et al 1999; Abicht et al 2002]. In addition, a chromosomal microdeletion of 1290 bp encompassing parts of *CHRNE* has been shown to result in CMS [Abicht et al 2002]. One particular point mutation of the AChRε subunit (ε1267delG) resulting in endplate AChR deficiency has been shown to be common (~50%) in affected individuals of Romany and/or southeastern European ethnic origin [Abicht et al 1999, Karcagi et al 2001]. The prevalence of this mutation appears to be very high due to a founder effect in the Romany population [Morar et al 2004]. Another mutation of the AChR epsilon subunit (ε1293insG) may be frequent in the Maghreb (especially Algeria and Tunisia) because of an ancient founder effect [Beeson et al 2005].

Normal gene product: The five homologous subunits of the adult AChR (two αsubunits, and one each of β, δ, and ε) each have a large N-terminal extracellular domain and four transmembrane segments (M1-M4); the M2 domain lines the cation-selective pore.

Abnormal gene product: Morphologic studies of endplates show an increased number of endplate regions distributed over an increased span of the muscle fiber. The integrity of the junctional folds is preserved, but AChR expression on the folds is patchy and faint. The fetal type γsubunit may partially compensate for absence of the εsubunit and thereby ameliorate the phenotype.

Mutations in the gene encoding rapsyn

Normal allelic variants: The gene *RAPSN* encoding the postsynaptic protein rapsyn consists of eight exons.

Pathologic allelic variants: In four individuals with endplate AChR deficiency but with no mutations in AChR subunits, three recessive *RAPSN* mutations (missense and frameshifting) have been identified [Ohno et al 2002, OMIM 601592]. No fewer than 21 mutations in *RAPSN* have been identified to date in the coding region (missense, frameshift, stop, and splice site mutations) and the promoter region (see Ohno & Engel 2004a and Engel & Sine 2005). The missense mutation N88K has been identified in all individuals with mutations in the translated region in at least one allele. Other mutations in the translated region are dispersed over different domains of the protein. There is evidence for an ancient Indo-European founder [Richard et al 2003; Müller, Abicht, Burke et al 2004] but not all affected individuals with N88K have the same haplotype [Richard et al 2003, Ohno & Engel 2004b]. One affected individual was found to be a compound heterozygote with the N88K mutation on one *RAPSN* allele and a large (~4.5-kb) deletion disrupting the other *RAPSN* allele [Müller, Abicht, Christen et al 2004].

Normal gene product: Rapsyn, a 43-kd postsynaptic protein, plays an essential role in the clustering of AChR at the endplate. It self-associates, aggregates AChRs, and links them to the subsynaptic cytoskeleton.

Abnormal gene product: EP studies in each case have shown decreased staining for rapsyn and AChR, as well as impaired postsynaptic development. Expression studies of mutant constructs indicate that all mutations diminished co-clustering of AChR with rapsyn.

Mutations in the gene encoding MuSK

Normal allelic variants: *MUSK* consists of 14 exons.

Pathologic allelic variants: Recently, two heteroallelic mutations (frameshift and missense) were identified in a single individual with CMS. Muscle biopsy showed dramatic pre- and postsynaptic structural abnormalities of the neuromuscular junction and severe decrease in acetylcholine receptor (AChR) epsilon-subunit and MuSK expression [Chevessier et al 2004].

Normal gene product: The gene *MUSK* encodes the postsynaptic muscle-specific receptor tyrosine kinase. The muscle-specific receptor tyrosine kinase MuSK plays an essential role in the agrin-MuSK-rapsyn pathway in organizing the postsynaptic scaffold and in inducing the high concentration of AChR and tyrosine kinases of the ErB family in the postsynaptic membrane.

Abnormal gene product: Expression studies of mutant constructs have indicated that the frameshift mutation prevents MuSK expression; that the missense mutation diminishes the expression and stability of MuSK but not its kinase activity; and that overexpression of the missense mutant in mouse muscle results in decreased EP AChR and aberrant axonal outgrowth [Chevessier et al 2004].

Mutations in the gene encoding the voltage-gated sodium channel of skeletal muscle ($Na_v1.4$)

Normal allelic variants: The gene *SCN4A* consists of 24 exons.

Pathologic allelic variants: Only one individual with CMS and two heteroallelic mutations (V1442E and S246L) in *SCN4A* has been observed to date [Tsujino et al 2003]. The individual

was a 20-year old normokalemic woman with eyelid ptosis, marked generalized fatigable weakness, and recurrent attacks of respiratory and bulbar paralysis since birth that caused anoxic brain injury. Intercostal muscle studies revealed that endplate potentials depolarizing the resting potential to 240 mV failed to excite action potentials. Several other gain-of-function mutations of *SCN4A* have been identified in a variety of disorders of muscle membrane excitability: potassium-aggravated myotonia, paramyotonia congenita, and hyperkalemic periodic paralysis (for review, see Cannon 2000).

Normal gene product: The gene *SCN4A* encodes the voltage-gated sodium channel of skeletal muscle ($Na_v1.4$) which mediates the voltage-dependent sodium ion permeability of the postsynaptic membrane to generate and propagate an action potential.

Abnormal gene product: Expression studies on the observed mutations in HEK cells revealed that the V1442E Na channel showed marked enhancement of fast inactivation close to the resting potential and enhanced use-dependent inactivation on high frequency stimulation; S246L showed only minor kinetic abnormalities, suggesting that it is a benign polymorphism. $Na_v1.4$ expression at the endplates and over the sarcolemma was normal by immunocytochemical criteria [Tsujino et al 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.

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Muscular Dystrophy Association (MDA)
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Phone: 800-FIGHT-MD (800-344-4863); 520-529-2000
Fax: 520-529-5300
Email: mda@mdausa.org
www.mdausa.org

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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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Chapter Notes

Revision History

- 26 September 2006 (aa) Revision: clinical testing available for: mutation scanning of *RAPSN*, *CHAT*, *COLQ*, *CHRNB1*, and *CHRND*; sequence analysis of *CHRNE* and *CHRNA1*; targeted mutation analysis of *RAPSN* mutation p.N88K, *CHAT* mutation

p.I305T, and *CHRNA1* mutation p.G153S; prenatal diagnosis for *CHAT*, *CHRNA1*, *CHRNB1*, *CHRND*, *CHRNE*, *COLQ*, and *RAPSN*

- 20 September 2005 (aa) Revision: sequence analysis for *RAPSN* clinically available
- 8 August 2005 (me) Comprehensive update posted to live Web site
- 9 May 2003 (me) Review posted to live Web site
- 30 January 2003 (aa) Original submission

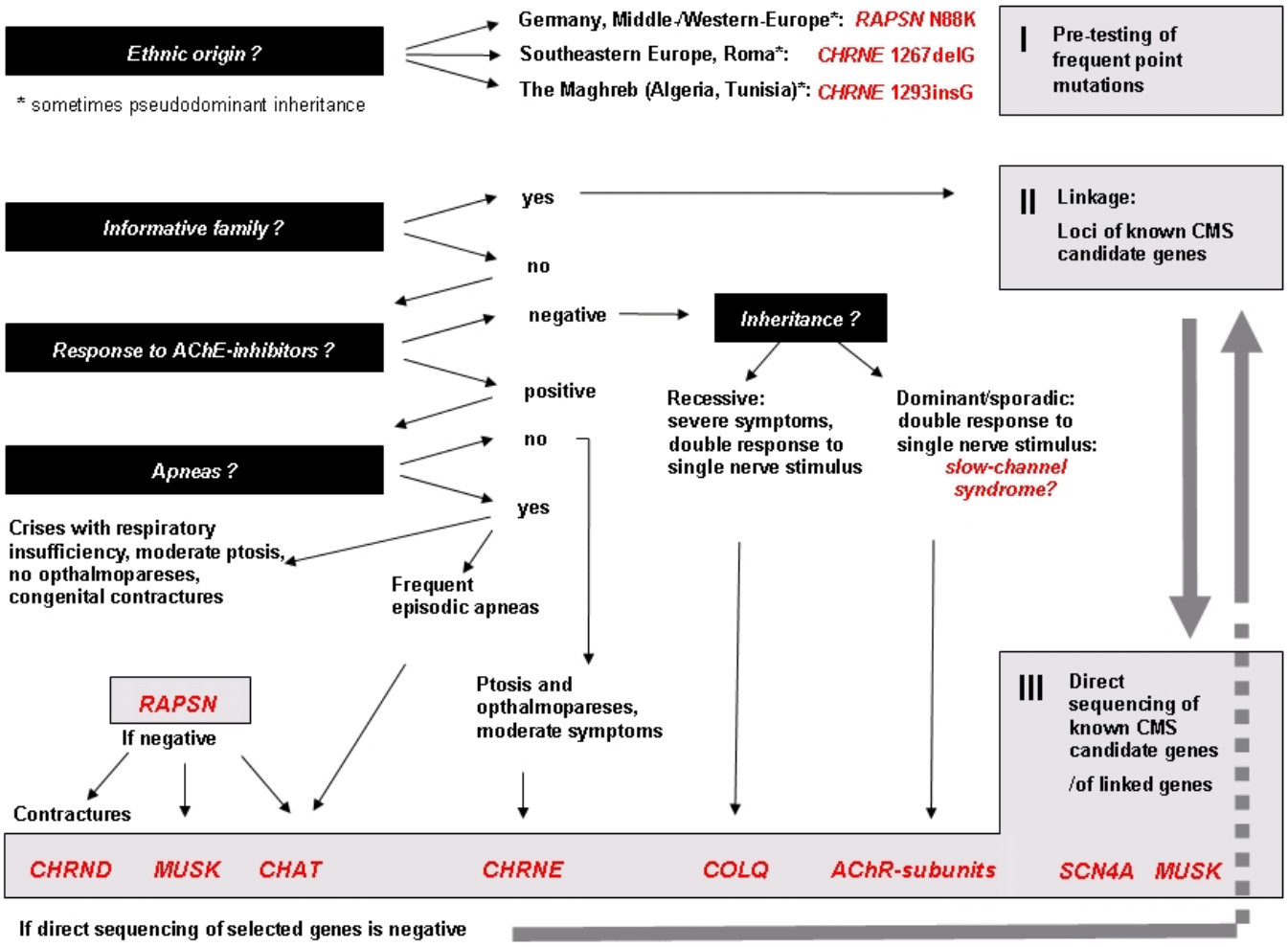

Figure 1. CMS Genetic Testing Algorithm