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Cold-Induced Sweating Syndrome Including Crisponi Syndrome

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Summary

Clinical characteristics

Cold-induced sweating syndrome (CISS) and its infantile presentation, Crisponi syndrome(CS) is characterized by dysmorphic features (distinctive facies, lower facial weakness, flexion deformity at the elbows, camptodactyly with fisted hands, misshapen feet, and overriding toes); intermittent contracture of facial and oropharyngeal muscles when crying or being handled with puckering of lips and drooling of foamy saliva often associated with laryngospasm and respiratory distress; excessive startling and opisthotonus-like posturing with unexpected tactile or auditory stimuli; poor suck reflex and severely impaired swallowing; and a scaly erythematous rash. During the first decade of life, children with CISS/CS develop profuse sweating of the face, arms, and chest with ambient temperatures below 18° to 22° C, and with other stimuli including nervousness or ingestion of sweets. Affected individuals sweat very little in hot environments and may feel overheated. Progressive thoracolumbar kyphoscoliosis occurs, requiring intervention in the second decade.

Diagnosis/testing

The diagnosis of CISS/CS is established in a proband with suggestive findings and biallelic pathogenic variants in either *CLCF1* or *CRLF1* identified on molecular genetic testing

Management

Treatment of manifestations: Supplemental oxygen is needed for laryngospasm with respiratory distress and cooling blankets for bouts of hyperthermia; intervention for feeding difficulties is necessary over the first year of life; bracing and physical therapy for camptodactyly and prolonged bracing or surgical intervention may be required to treat a progressive thoracolumbar scoliosis. Topical lubrication needed to avoid corneal alterations and regular dental care needed to avoid excessive dental decay. Options for the treatment of cold-induced sweating include clonidine alone, clonidine plus amitryptyline, or moxonidine alone.

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Surveillance: Evaluate for scoliosis. Ophthalmologic evaluation for corneal injury every six months and yearly dental visits due to early dental decay are recommended.

Agents/circumstances to avoid: Heat exposure and prolonged physical activity in a hot climate.

Pregnancy management: Pharmacologic treatments for cold-induced sweating should be discontinued during pregnancy, as teratogenic effects on the fetus have not been well studied and remain a possibility. The prescription of clonidine should not be discontinued abruptly; the drug should be phased out over four to six days.

Genetic counseling

CISS/CS is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *CLCF1* or *CRLF1* pathogenic variant, each sib of an affected individual has at conception 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 the *CLCF1* or *CRLF1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Cold-induced sweating syndrome (CISS) and its infantile presentation, Crisponi syndrome (CS) **should be suspected** in individuals with the following cardinal clinical characteristics:

- **Dysmorphic features present at birth** (Figure 1A, Figure 1B) including:
  - Round face
  - Chubby cheeks
  - Low-set ears
  - Depressed nasal bridge and anteverted nares
  - Long philtrum, high-arched palate, and micrognathia
  - Cubitus valgus and flexion deformity at the elbows
  - Fisted hands, camptodactyly, overriding fingers, and transverse palmar creases
  - Misshapen feet and overriding toes
- **Characteristic facial expression** (Figure 1A, Figure 2A) including:
  - Intermittent contracture of facial and oropharyngeal muscles when crying or being handled, with puckering of the lips and drooling of foamy saliva
  - Normal facial expression when relaxed or sleeping (Figure 1B)
  - Typically, excessive startling and opisthotonus-like posturing with unexpected tactile stimuli or loud noises (Figure 3)
- **Poor suck reflex and severely impaired swallowing present at birth**
  - Marked difficulty feeding that may necessitate nasogastric or gastrostomy tube feeding
  - Mild lower facial weakness that usually persists throughout life (Figure 2B)
- **Scaly erythematous rash** (Figure 2A)
  - Present in infancy and persisting throughout early childhood
  - Affecting the face, fingers, and occasionally trunk
- **Paradoxic, cold-induced sweating with onset in the first decade**
  - Profuse sweating on the face, arms, and anterior and posterior chest to the waist at environmental temperatures below 18°-22° C (64°-71° F) or on exposure to a cold draft or cold drink

- Sweating is also observed with nervousness and ingestion of sweets (illustrated in Hahn et al [2006]).
- **Other thermoregulatory abnormalities**
  - Minimal sweating in heat (limited to the lumbar region, groin, and thighs) that may result in uncomfortable overheating
  - In infancy, recurrent temperature spikes up to 42° C (108° F), not associated with infections, leading, in some children, to seizures and at times, to sudden death
- **Progressive thoracolumbar kyphoscoliosis** requiring bracing or surgical intervention in the second decade

Establishing the Diagnosis

The diagnosis of CISS/CS **is established** in a proband with suggestive findings and biallelic pathogenic variants in either *CLCF1* or *CRLF1* on molecular genetic testing (see Table 1).

Note: Identification of biallelic *CLCF1* or *CRLF1* variants of uncertain significance (or identification of one known *CLCF1* or *CRLF1* pathogenic variant and one *CLCF1* or *CRLF1* variant of uncertain significance) does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of CISS/CS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A multigene panel that includes *CLCF, CRLF1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

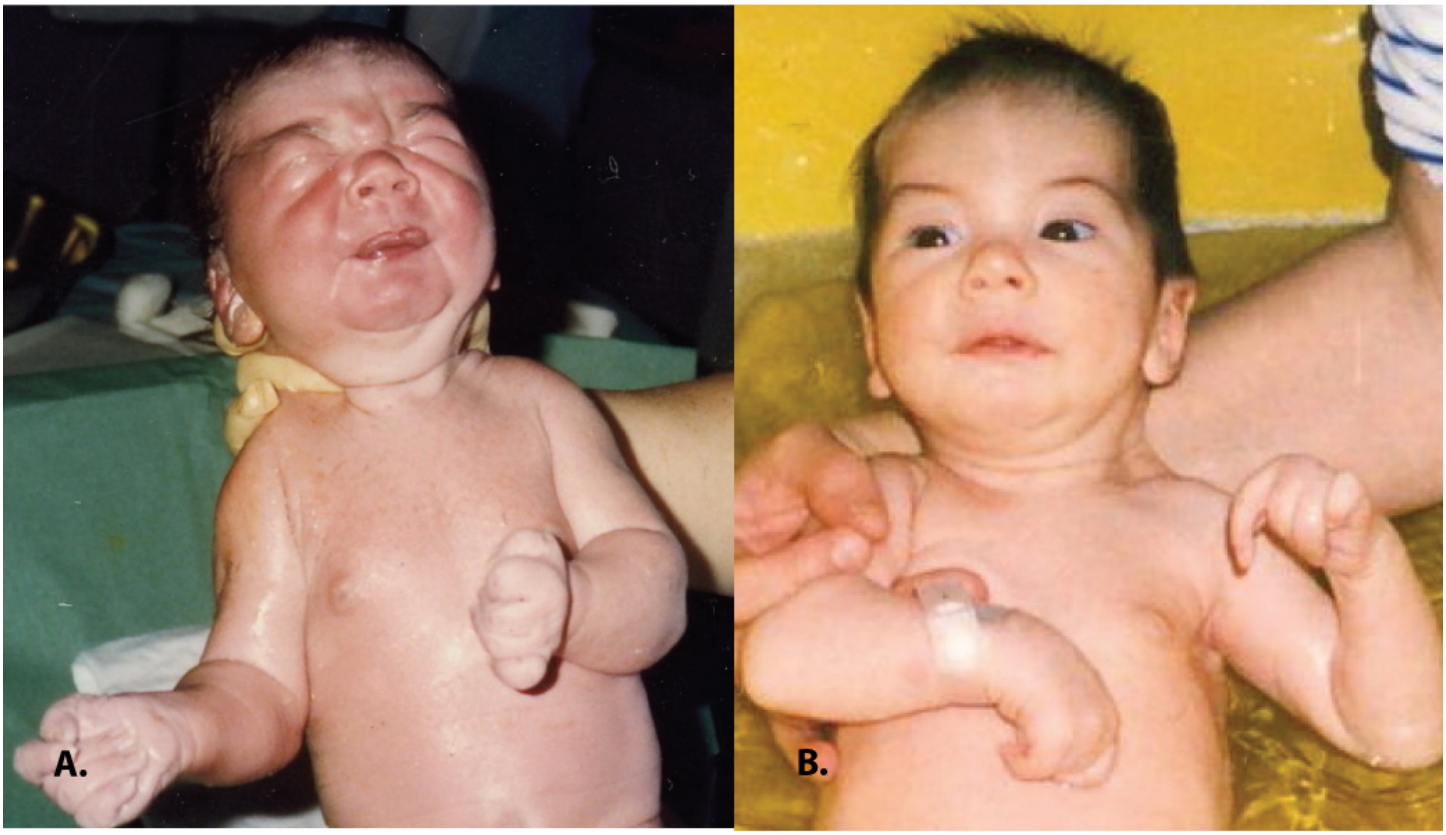

Figure 1. A. Newborn with Crisponi syndrome, caused by biallelic *CRFL1* pathogenic variants, showing camptodactyly with fisted hands and characteristic facial features (rounded face, poorly developed and depressed nasal bridge, anteverted nares, long philtrum, facial grimacing, and tightly pursed lips).

B. Same infant at age three months in a relaxed state without the facial grimacing.

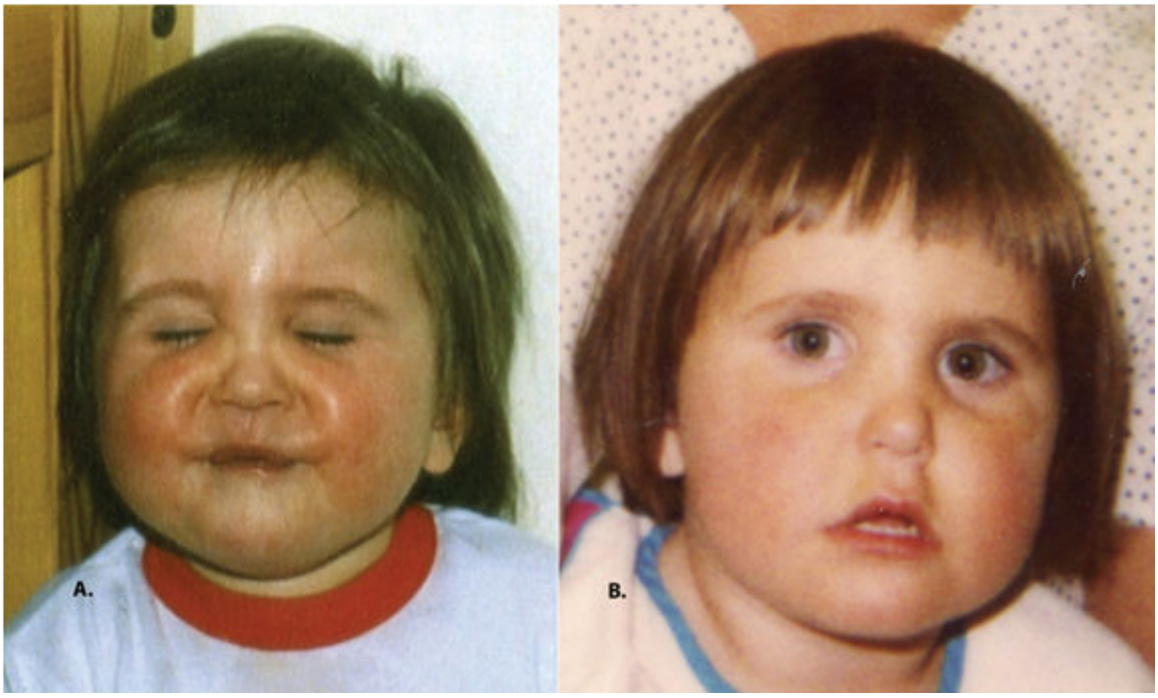

Figure 2. A. Girl age 18 months with Crisponi syndrome, caused by biallelic *CLCF1* pathogenic variants, demonstrating typical facial muscle contraction and puckering of the lips. Note the characteristic erythematous rash over the cheeks.

B. Younger sister to A at a similar age; note the signs of lower facial weakness in the perioral region. She also has a facial rash.

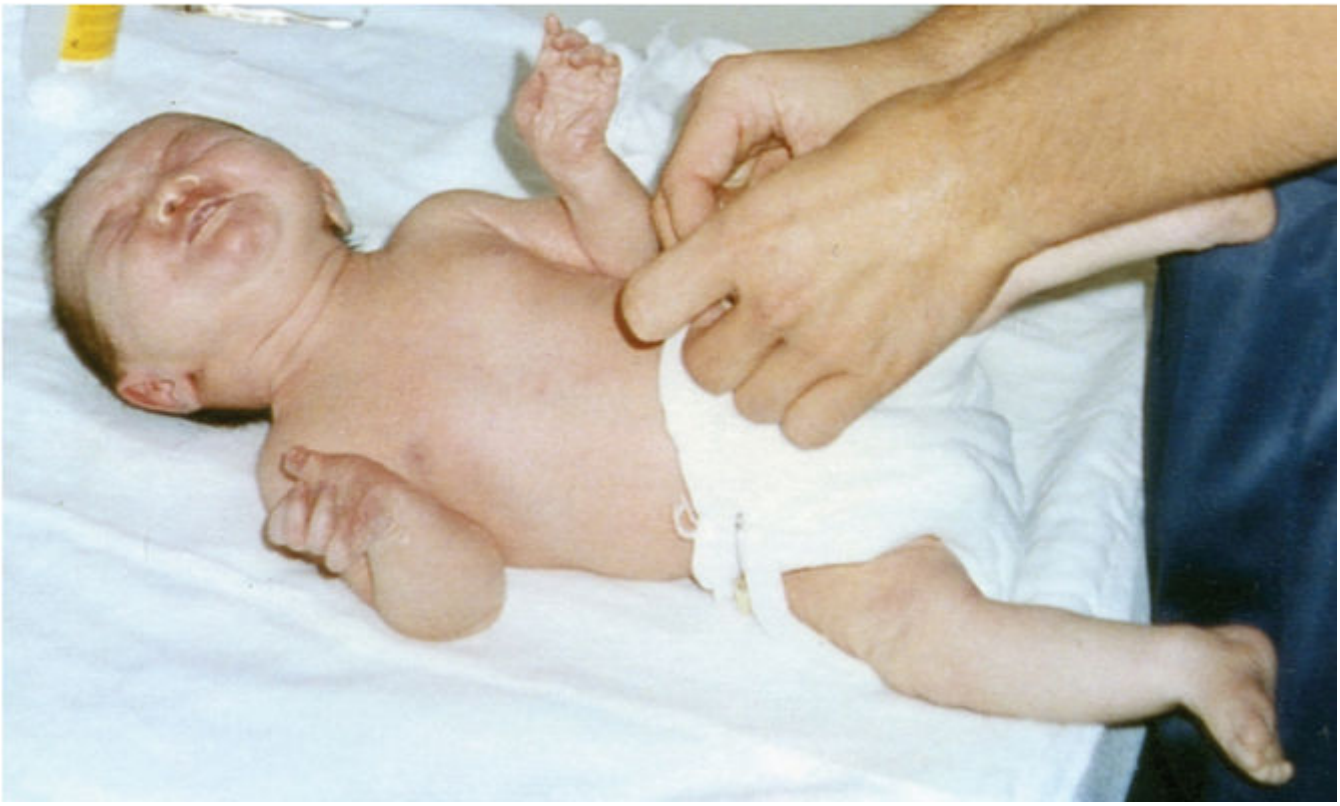

Figure 3. Infant with Crisponi syndrome, caused by *CLCF1* biallelic pathogenic variants, demonstrating the tendencies to grimace and startle while being handled. The infant assumes an extensor posture, retracting the head and raising and flexing the arms.

Table 1. Molecular Genetic Testing Used in Cold-Induced Sweating Syndrome/ Crisponi Syndrome (CISS/CS)

Gene [1, 2]	Proportion of CISS/CS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
CLCF1	~5%	5/5 [6, 7]	Unknown [8]
CRLF1	~95%	~99% [6]	~1% [6, 9]

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
7. Five distinct *CLCF1* pathogenic variants were found in four individuals from three families [Hahn et al 2010, Buers et al 2020b].
8. No data on detection rate of gene-targeted deletion/duplication analysis are available.
9. Seven large deletions/duplications involving parts or all of *CRLF1* have been reported [Di Leo et al 2010; Buers et al 2020a; Schierz et al 2020; Authors, personal observation]. For more information on these pathogenic variants, contact the authors.

Clinical Characteristics

Clinical Description

Cold-induced sweating syndrome (CISS) can present to the clinician in infancy as Crisponi syndrome, or from age three years onward as cold-induced sweating syndrome. Interviews with mothers of children or adults with CISS, review of a targeted questionnaire completed by caregivers of the infants, and review of early medical records revealed that probably **all** individuals had findings of CS in infancy, some more severe than others [Hahn et al 2010].

To date, 99 individuals have been identified with biallelic pathogenic variants in either *CLCF* or *CRLF1* [Hahn et al 2010; Buers et al 2020a; Buers et al 2020b; Schierz et al 2020; Authors, personal observations]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Cold-Induced Sweating Syndrome / Crisponi Syndrome (CISS/CS): Frequency of Select Features

Feature		% of Persons with Feature	Comment
Infantile period	Dysmorphic facial features	100%	
	Poor suck & swallow, micrognathia, restricted jaw movements	100%	
	Excessive startling when crying, being handled, or w/loud noises	90%	Assoc w/an opisthotonos-like posture, tightly pursed lips, & excessive foamy salivation
	Facial-oral-laryngospasms assoc w/respiratory distress	~60%	Assoc w/startle
	Bouts of hyperthermia	90%	Isolated temperature spikes up to 42°C (108° F) w/o infections
	Camptodactyly &/or flexion deformity at elbows	80%	
	Misshapen feet, overriding toes	~50%	
	Scaly erythematous skin rash	~20%	
Childhood/ Adulthood	Gradual improvement of swallowing & feeding by end of 1st yr	~100%	
	Persistent lower facial weakness	~90%	
	Impaired thermoregulation	100%	
	Paradoxic cold-induced sweating	100%	
	Heat intolerance	100%	
	Progressive thoracolumbar kyphoscoliosis	90%	

Presentation in Infancy (Crisponi Syndrome)

Typical dysmorphic features (see Suggestive Findings) are noted at birth and are accompanied by an inability to suckle and swallow due to facial and bulbar weakness and the presence of micrognathia and restricted jaw movements. Intermittently, infants show characteristic facial-oral contractions, with tightly pursed lips and excessive salivation; these are not observed when relaxed or during sleep (Figure 1A, Figure 1B).

Excessive startle. When crying or being handled or with loud noises, infants tend to startle excessively; they transiently assume an opisthotonus-like posture with extended neck, flexed arms and fisted hands. At the same time, they show characteristic facial contractions and may also develop laryngospasm and difficulty breathing, with circumoral cyanosis as a sign of anoxia.

Life-threatening events. Respiratory difficulties and unexplained high fevers up to 42° C [108° F] can lead to seizures and sudden death. Crisponi [1996] originally described this presentation in 17 newborns from 12 families of southern Sardinia. As 15 of the infants died in the first few months, the condition was considered to have a poor prognosis. However, it is now recognized that survival past infancy can be expected with attentive care, as most early-infantile problems disappear gradually over the first two years of life.

Feeding issues. Affected infants usually begin to feed normally by age one to two years. Occasionally, dysphagia persists throughout the first decade and may be associated with lack of interest in food or liquids. Gastroesophageal reflux may occur.

Neurodevelopmental findings. Excessive startling disappears by age two years. Psychomotor and speech development can be delayed due to manual difficulties caused by camptodactyly and orofacial weakness, respectively [Hahn et al 2010].

It is important to note that the seizures noted in infants with this disorder occur in association with hyperthermia and not as a primary seizure disorder.

Corneal injury. Decreased blink rate and incomplete eye closure in sleep due to facial muscle weakness predisposes for exposure keratitis and corneal scarring.

Orthopedic findings include camptodactyly of the fingers and flexion contractures of the elbows; hands are often fisted.

Skin findings. A scaly erythematous rash on the face, trunk and limbs is present in infancy and persists through early childhood.

Early dental decay to the point of complete loss of teeth in the second decade has been observed.

Presentation in Childhood and Adulthood

Persistent lower facial weakness. Decreased mimical expression, open mouth position, horizontal smile, and nasal speech have been observed in childhood and beyond.

Impaired thermoregulation

- **Cold-induced sweating**, the most disabling symptom in adulthood, is recognized during the first decade (from age 3 years onward). At environmental temperatures of ≤22°C (72° F), affected individuals sweat profusely on their face, arms (sparing the palms) and upper body, accompanied by intense shivering and dermal vasoconstriction, so that the fingers appear cold and cyanotic.
- **Profuse sweating** is also triggered by apprehension or nervousness or by sweet gustatory stimuli, in particular by chocolate.
- **Heat intolerance.** In contrast, affected individuals sweat very little in heat and only in the lumbar region, the groin, and the anterior thigh. They become flushed and unpleasantly overheated in hot climates [Hahn et al 2006, Hahn et al 2010]. Although the hyperhidrosis can be effectively treated [Hahn et al 2006, Hahn et al 2010, Herholz et al 2010], heat intolerance is a lifelong problem.

Scoliosis. Toward the end of the first decade, affected children develop progressive thoracolumbar kyphoscoliosis that requires either bracing or spinal instrumentation.

Decreased tactile, temperature, and pain perception. Decrease in perception of light touch, temperature, and painful stimuli and atrophy of small foot muscles have been observed in some individuals [Knappskog et al 2003], indicating a mild chronic axonal sensory and motor peripheral neuropathy. In a study by Hahn et al [2006], sensory and motor nerve conduction velocities recorded from sural nerves and from peroneal nerves were normal, but the evoked sensory and motor action potential amplitudes were reduced [Hahn et al 2006]. This altered sensory perception may be accounted for by the findings of length-dependent derangement of somatic sensory innervation found in skin biopsies derived from fingers and distal legs [Di Leo et al 2010].

Other Findings

Laboratory tests, metabolic studies, and detailed studies of autonomic functions are normal, with the exception of sudomotor functions [Hahn et al 2006]. EEG and brain MRI are normal. Rarely a thin corpus callosum and delayed white matter myelination has been described.

Prognosis

Once the difficulties of early childhood have been overcome, individuals with CISS/CS are for the most part able to lead a fairly normal and productive life, obtain a secondary education, and have children. Life expectancy is probably normal; to date only one individual has been followed to the eighth decade [Hahn et al 2006].

Genotype-Phenotype Correlations

Clinical manifestations are identical in individuals with *CLCF1* or *CRLF1* pathogenic variants [Hahn et al 2010].

No genotype-phenotype correlations for either *CLCF1* or *CRLF1* have been identified [Piras et al 2014].

Nomenclature

The term "cold-induced sweating syndrome" was coined [Knappskog et al 2003] from the title of the Lancet report "cold-induced profuse sweating on back and chest" [Sohar et al 1978].

Following the demonstration of locus heterogeneity, the abbreviations CISS1 and CISS2 were introduced [Hahn et al 2006]. As CISS1 and CISS2 are clinically indistinguishable, the term "CISS" covers both disorders until a molecular diagnosis is made.

With time, survivors of infantile-onset Crisponi syndrome [Crisponi 1996] will develop CISS, substantiated by the identification of pathogenic variants in *CRLF1* [Buers et al 2020a] or *CLCF1* [Hahn et al 2006, Hahn et al 2010]. Thus, CISS and Crisponi syndrome are not "allelic disorders," but rather Crisponi syndrome is the infantile presentation of CISS [Dagoneau et al 2007, Hahn et al 2010].

Prevalence

CISS/CS has been observed in individuals originating from every continent except Africa. *CRLF1*-associated CISS/CS appears to be particularly prevalent in the Mediterranean region [Piras et al 2014, Buers et al 2020a].

To date only four individuals with *CLCF1*-associated CISS/CS have been reported [Hahn et al 2010, Buers et al 2020b].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CRLF1* or *CLCF1*.

Differential Diagnosis

The primary disorder of interest in the differential diagnosis of cold-induced sweating syndrome / Crisponi syndrome (CISS/CS) is Stüve-Wiedemann syndrome (STWS). STWS and CISS/CS share the same pathogenic mechanism [Di Leo et al 2010, Melone et al 2014], and apart from the bone abnormalities associated with STWS, the disorders are identical.

STWS and other disorders in the differential diagnosis of CISS/CS are summarized in Table 3.

Table 3. Genes and Disorders of Interest in the Differential Diagnosis of Cold-Induced Sweating Syndrome / Crisponi Syndrome (CISS/CS)

Gene	Disorder	MOI	Clinical Characteristics & Overlapping Features	Distinguishing Features
KLHL7	PERCHING syndrome (OMIM 617055)	AR	Infants w/PERCHING syndrome may resemble those w/CISS/CS: both disorders are assoc w/paroxysmal oropharyngeal muscle contractions, swallowing & feeding difficulties, typical dysmorphic features, & camptodactyly. [1] Some persons w/ PERCHING syndrome have hyperthermia & signs of retinitis pigmentosa.	Unlike CISS/CS, few persons w/ PERCHING syndrome survive childhood, & none has demonstrated cold-induced sweating.

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Characteristics & Overlapping Features	Distinguishing Features
LIFR [2]	Stüve-Wiedemann syndrome (STWS) (OMIM 601559)	AR	Dysmorphic facial features; camptodactyly; severe sucking, swallowing, & feeding difficulties; stimulus-induced abnormal posturing & episodic facial contractions; laryngospasm causing respiratory distress; episodes of hyperthermia & sudden death. [2] Persistent heat intolerance & paradoxic cold-induced sweating. [3] Teens may manifest ↓ pain perception, signs of corneal injuries & scarring, early dental decay, & progressive kyphoscoliosis.	Chondrodysplasia (manifest as congenital bowing of the long bones & ↓ joint mobility) is the main differentiating characteristic. (Note: STWS w/cold-induced sweating but w/o bowing of long bones has been reported. [4])
MAGEL2	Schaaf-Yang syndrome (SYS)	AD [5]	Neurodevelopmental disorder similar to Prader-Willi syndrome. Manifest at birth w/ generalized hypotonia, sucking & feeding difficulties, episodic severe respiratory distress & sleep apnea, & distal joint contractures. Children show marked DD & speech delay, & exhibit autistic behavior & ID.	Infants w/SYS do **not** present w/ characteristic dysmorphic features, episodic facial contractions, or stimulus-induced posturing typical of CISS/CS. SYS is not assoc w/ hyperthermia or impaired thermoregulation.
MYH3	Distal arthrogryposis types 2A & 2B (DA2A/DA2B) (OMIM 193700 & 601680)	AD	**Severe** distal arthrogryposis & joint contractures; "whistling face" (intermittent facial muscle contraction & puckering of lips) that may resemble facial movements in young children w/CISS/CS	In infants w/CISS/CS (but not in DA2A/DA2B), puckering of lips is provoked by crying. In DA2A/DA2B, puckering of lips may occur when resting or sleeping. Microstomia (seen in DA2A/DA2B) is not assoc w/ CISS/CS.
NALCN	Congenital contractures of the limbs & face, hypotonia, & DD (CLIFAHDD) (OMIM 616266)	AD	Striking similarity w/CISS/CS: facial dysmorphisms, distal arthrogryposis & camptodactyly; micrognathia, impaired sucking, swallowing, & feeding w/need for long-term NG tube feeding; episodic stimulus-induced facial & oropharyngeal contractions, pursing of lips & excessive salivation, inspiratory stridor, & hypoxemia. Spells occur only during waking & incl excessive sweating in face, head, & upper trunk. [7]	Unlike CISS/CS, CLIFAHDD is assoc w/persistent severe axial hypotonia, precarious respiratory status, & DD.

AD = autosomal dominant; AR = autosomal recessive; CISS = cold-induced sweating syndrome; CS = Crisponi syndrome; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; NG = nasogastric

1. Angius et al [2016]

2. Mikelonis et al [2014]

3. Gaspar et al [2008]

4. Melone et al [2014] reported a female age 33 years with features of STWS including cold-induced sweating, but without bowing of the long bones and complete chromosome 5 maternal isodisomy with an isozygous *LIFR* pathogenic variant (c.2170C>G, p.Pro724Ala). The proband's mother was heterozygous for the c.2170C>G variant.

5. Schaaf-Yang syndrome is inherited in an autosomal dominant, maternally imprinted manner (i.e., a heterozygous pathogenic variant on the paternally derived *MAGEL2* allele results in disease; a pathogenic variant on the maternally derived *MAGEL2* allele does not result in disease because normally the maternally derived *MAGEL2* allele is silenced).

6. McCarthy et al [2018]

7. Chong et al [2015], Lozic et al [2016]

Management

Clinical practice guidelines for cold-induced sweating syndrome / Crisponi syndrome (CISS/CS) have been published in Buers et al [2020a] and are detailed in this section.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with CISS/CS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Note: Any evaluation of an infant needs to proceed with extreme care in handling to avoid startling the infant, which can result in laryngospasm. Supplemental oxygen and a cooling blanket need to be readily available at the bedside.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Cold-Induced Sweating Syndrome / Crisponi Syndrome (CISS/CS)

Diagnosis	System/Concern	Evaluation	Comment
In infancy	**Need for controlled environment**	Evaluate for ways to keep infant in quiet & calm environment w/temperature control (20° C).	Careful handling is essential to avoid excessive startling & spasm; infants are typically irritable.
	Respiratory status	Oxygen saturation test	
	Hydration status	Physical exam & electrolyte testing	Infants w/CISS/CS may be dehydrated at presentation/diagnosis.
	Safety of oral feeding	• Swallowing test • Esophageal manometry	
	Neurologic status	Assessment by neurologist	
		EEG if seizures observed	Seizures occur in response to hyperthermia, not as a primary disorder.
	Reduced corneal sensitivity	Assessment by ophthalmologist for corneal injury	
	Flexion contractures of fingers & elbows	Assessment by PT or OT	

Table 4. continued from previous page.

Diagnosis	System/Concern	Evaluation	Comment
In childhood or adulthood	**Neurologic status**	Assessment by neurologist	
	Impaired thermoregulation [1]	Review symptoms w/patient & family.	Normally noted by parents but not a concern until early teens
	Scoliosis	Assess spine w/radiographs & exam.	
	Genetic counseling	By genetics professionals [2]	To inform patients & families re nature, MOI, & implications of CISS/CS in order to facilitate medical & personal decision making
	Family support & resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	

MOI = mode of inheritance; OT = occupational therapist; PT = physical therapist
1. Including cold-induced sweating, profuse sweating triggered by other stimuli, & heat intolerance
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Management by multidisciplinary specialists including neonatologist, pediatrician, neurologist, geneticist, gastroenterologist, dermatologist, orthopedist, hand surgeon, dietician, physical therapist, occupational therapist, speech therapist, psychologist, dentist is recommended.

Infants with CISS/CS are extremely fragile and require special care, including the following:

- Continuous monitoring of cardiorespiratory parameters with supplementary oxygen readily available
- Room temperature or incubator temperature constant at 20° C
- Quiet and somewhat darkened room
- Gentle handling for diaper changes and turning
- Minimized painful stimuli such as venipunctures
- Preparedness for hyperthermic crisis (cooling blankets on site)
- Preparedness for seizures (associated with hyperthermia) and respiratory distress

Other specific treatments are listed in Table 5.

Table 5. Treatment of Manifestations in Individuals with Cold-Induced Sweating Syndrome / Crisponi Syndrome (CISS/CS)

Manifestation/Concern	Treatment	Considerations/Other
Laryngospasm w/respiratory distress	Provide for supplemental oxygen w/o delay.	An apnea monitor is recommended.
Bouts of hyperthermia (≤42° C [108° F])	Cooling blankets	Temperature-reducing medications are not effective.
Seizures	Anti-seizure medication for acute episodes	Long-term seizure medication past the infantile period will seldom be necessary as seizures are symptomatic of hyperthermia, not due to a primary seizure disorder.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Feeding difficulty in infancy	NG or gastrostomy tube feeding until disorganized swallowing & esophageal dysmotility improve over 1st year of life	Manage gastroesophageal reflux pharmacologically.
Camptodactyly	Bracing & PT/OT	Plastic surgery may be considered at a later stage.
Thoracolumbar scoliosis	Prolonged bracing or surgical correction depending on rapidity of progression	
Corneal injury	Topical lubrication w/artificial tears at daytime, lubricating gels at night	For severe corneal injury, tarsorrhaphy can be considered.
Dental decay	Regular dental visits	W/focus on prevention of early dental decay
Paradoxic cold induced sweating in older children & adults	See Pharmacologic Management of Cold-Induced Sweating.	Normally noted by parents (w/earliest start at 2 yrs) but not a concern in childhood; treatment can be delayed until early teens.
Heat intolerance (lack of sweating)	Cold drinks, splashing self w/or immersing in cold water	Avoid prolonged exposure to or physical activities in hot environmental temperatures.
Lack of temperature & pain sensation in fingers & toes	Patients should be made aware of the risks of burns or frostbite.	Wear clothing (e.g., mittens & socks) to protect against burns & frostbite.

NG = nasogastric; OT = occupational therapy; PT = physical therapy

Pharmacologic Management of Cold-Induced Sweating

Options for the treatment of cold-induced sweating include clonidine alone, clonidine plus amitriptyline, or moxonidine alone.

Before initiating any of these medications, the potential interaction with already-prescribed medications should be assessed. If there are no contraindications, the drugs should be maintained at the lowest dose required for acceptable symptom control.

Recommended regimen is as follows:

1. Start with clonidine alone. **Oral clonidine starting dose** is 0.05 mg to 0.1 mg twice daily.
    - This dose is usually well tolerated and will effectively reduce or abolish sweating.
    - The beneficial effects of clonidine may lessen within a few weeks due to habituation.
    - If necessary, increase the daily dose gradually in steps of 0.05 mg twice daily to effectiveness and tolerance to a maximum dose of 0.1 mg four times daily.
    - Side effects include dry mouth, sedation, and postural hypotension (can be mitigated by increased salt and fluid intake).
    - If clonidine needs to be discontinued, it should be phased out over six days; abrupt cessation of clonidine can lead to rebound hypertension.
2. If control of sweating is insufficient at the tolerated dose of clonidine, amitriptyline may be added. **Oral amitriptyline starting dose** is 10 mg orally at bedtime combined with the tolerated dose of clonidine.

    The dose of amitriptyline may need to be increased to a maximum of 25 mg four times daily (taken with clonidine).

3. If combined clonidine plus amitriptyline is not tolerated or not effective, moxonidine alone can be tried [Herholz et al 2010]. **Moxonidine as a single drug** at a maximal oral dose of 6 µg/kg/d can provide adequate symptom control and is usually well tolerated.

Prevention of Primary Manifestations

See Treatment of Manifestations.

Surveillance

Table 6. Recommended Surveillance for Individuals with Cold-Induced Sweating Syndrome / Crisponi Syndrome (CISS/CS)

System/Concern	Evaluation	Frequency
Nutrition	• Nutritionist to evaluate growth parameters to assess success of feeding strategies • Gastroenterologist eval may be required for assistance w/feeding or aspiration concerns.	1-2x/yr
Neurologic status	Neurologist follow up for seizures if present & for neurologic status & development	2x/yr or as needed
Psychomotor & speech delay	Neurodevelopmental eval to assess hand skills, speech development, oromotor skills (eating & chewing) & psychological adjustment	
Corneal injury	Ophthalmologic eval	1-2x/yr
Hand contractures	Physiotherapist exam	Every 3 mos
Rash & sweating issues	Monitoring by dermatologist	As required
Dental decay	Dental exam	Annually or as directed
Scoliosis	Orthopedic eval	2x/yr starting at end of 1st decade

Agents/Circumstances to Avoid

Affected individuals should avoid heat exposure and prolonged physical activity in a hot climate.

Evaluation of Relatives at Risk

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

Pregnancy Management

Females with CISS/CS may conceive normally. No complications during pregnancy have been reported to date.

Treatments for cold-induced sweating (clonidine, amitriptyline, moxonidine) should be discontinued during pregnancy, as the potential for teratogenic effects on the fetus is not well studied and remains possible. Clonidine should not be discontinued abruptly, but rather phased out over four to six days.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Cold-induced sweating syndrome / Crisponi syndrome (CISS/CS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *CRLF1* or *CLCF1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *CRLF1* or *CLCF1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *CRLF1* or *CLCF1* pathogenic variant, each sib of an affected individual has at conception 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with CISS/CS are obligate heterozygotes (carriers) for a pathogenic variant in *CRLF1* or *CLCF1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CRLF1* or *CLCF1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *CRLF1* or *CLCF1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.

- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *CRLF1* or *CLCF1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CISS/CS are possible.

Fetal ultrasound examination. In populations with documented *CRLF1* founder variants and an increased prevalence of CISS/CS, a prenatal diagnosis of CISS/CS may be suspected when evidence of camptodactyly is identified [Dessì et al 2012].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Cold-induced sweating syndrome

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Cold-Induced Sweating Syndrome including Crisponi Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CLCF1	11q13.2	Cardiotrophin-like cytokine factor 1	CLCF1 database	CLCF1	CLCF1
CRLF1	19p13.11	Cytokine receptor-like factor 1	CRLF1 database	CRLF1	CRLF1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Cold-Induced Sweating Syndrome including Crisponi Syndrome (View All in OMIM)

272430	CRISPONI/COLD-INDUCED SWEATING SYNDROME 1; CISS1
604237	CYTOKINE RECEPTOR-LIKE FACTOR 1; CRLF1
607672	CARDIOTROPHIN-LIKE CYTOKINE FACTOR 1; CLCF1
610313	CRISPONI/COLD-INDUCED SWEATING SYNDROME 2; CISS2

Molecular Pathogenesis

The ciliary neurotrophic factor receptor (CNTFR) pathway supports the differentiation and survival of a wide range of neuronal cell types (motor, sensory, and autonomic) during development and in adult life. CLCF1 and CRLF1 (encoded by *CLCF1* and *CRLF1* respectively) are secreted as a stable heterodimeric complex CRLF1/CLCF1 and act as a functional ligand to CNTFR. Pathogenic variants in *CLCF1* or *CRLF1* cause cold-induced sweating syndrome / Crisponi syndrome (CISS/CS) through failure of activation of the CNTFR pathway.

Mature sweat glands are known to be innervated by cholinergic sympathetic neurons. However, at birth immature sweat glands retain their embryonic noradrenergic sympathetic innervation. As sweat glands mature postnatally, they secrete a retrogradely acting cytokine which directs the innervating sympathetic neurons to change their transmitter phenotype from noradrenergic to cholinergic [Schotzinger et al 1994]. Members of the IL6 family of cytokines, in particular CLCF1 and CRLF1, were considered likely candidates to be involved in CISS/CS [Habecker et al 1997, Stanke et al 2006].

Skin biopsies from an individual with CISS associated with pathogenic variants in *CRLF1* demonstrated failure of cholinergic differentiation of sympathetic neurons innervating sweat glands [Di Leo et al 2010]. Skin biopsies from areas of cold-induced hyperhidrosis at the shoulder showed relatively preserved epidermal and dermal sensory innervation, yet sweat glands lacked the normally rich cholinergic innervation and retained instead an ample supply of noradrenergic sympathetic fibers. These observations suggested a failed switch of adrenergic to cholinergic sympathetic innervation of sweat glands, as the cause of paradoxic sweating.

Biopsies from the glabrous skin and from anhidrotic hairy skin (fingertip and leg, respectively) revealed length-dependent severe dermal sensory and autonomic denervation involving sweat glands and all skin adnexa, and the complete absence of cholinergic nerves, with few residual sweat glands and noradrenergic fibers present. These findings indicate a severe, possibly developmental derangement of cutaneous somatic and autonomic innervation, providing an explanation for the unusual reduction of sweating in the lower limbs and possibly also for the impaired pain perception reported in a proportion of individuals with CISS/CS [Knappskog et al 2003].

Infants with CISS/CS manifest lower facial weakness and inability to suckle and swallow. Mouse pups with targeted deletions of *Crlf1*, *Clcf1*, *Cntfr*, or *Lifr* display an identical phenotype and demonstrate inability to suckle. They die shortly after birth from malnutrition and are found to have a reduced number of facial and lumbar motor neurons [Forger et al 2003]. These observations exemplify that each component of the CNTFR signaling pathway plays an important role in early development and survival.

Mechanism of disease causation. The functional consequences of observed *CLCF1* and *CRLF1* pathogenic variants are primarily loss of function. The loss of function in one component of the CRLF1/CLCF1 complex leads to lack of activation of the CNTFRα/gp130/LIFR pathway and thereby to failure of downstream STAT3 signaling [Heinrich et al 2003, Rousseau et al 2006].

Gene-specific laboratory considerations: *CRLF1*

- Due to its high GC content of exon 1, *CRLF1* may be difficult to amplify and sequence. Adding of betaine or ^{3}GC-enhancer^{2} is recommended.
- The frequent p.Leu26del variant (allele frequency of 0.2 in gnomAD Database) may also cause problems in interpreting the exon 1 sequence; sequencing of both strands is recommended.

Table 7. Cold-Induced Sweating Syndrome / Crisponi Syndrome (CISS/CS): *CRLF1* Notable Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_004750.5 NP_004741.1	c.226T>G	p.Trp76Gly	Founder variant in Sardinia [Piras et al 2014] [2]
	c.676dupA (c.676_677dupA)	p.Thr226AsnfsTer104	Founder variant in Sardinia [Piras et al 2014] [2]
	c.713dupC	p.Pro239AlafsTer91	Founder variant in the Roma population (Spain) [Buers et al 2020a]
	c.242G>A / c.1121T>G	p.Arg81His / p.Leu374Arg	Persons of Israeli ancestry reported as homozygous for both variants [Knappskog et al 2003]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions
2. Together, the variants c.226T>G and c.676dupA are the most common in Sardinia, with a joint carrier frequency of 1.4% [Piras et al 2014].

Chapter Notes

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