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CTDP1-Related Congenital Cataracts, Facial Dysmorphism, and Neuropathy

Synonym: *CTDP1*-CCFDN

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Summary

Clinical characteristics

CTDP1-related congenital cataracts, facial dysmorphism, and neuropathy (*CTDP1*-CCFDN) is characterized by abnormalities of the eye (bilateral congenital cataracts, microcornea, microphthalmia, micropupils), mildly dysmorphic facial features apparent in late childhood, and a hypo-/demyelinating, symmetric, distal peripheral neuropathy. The neuropathy is predominantly motor at the onset and results in delays in early motor development, progressing to severe disability by the third decade of life. Secondary foot deformities and scoliosis are common. Sensory neuropathy develops after age ten years. Most affected individuals have a mild nonprogressive intellectual deficit and cerebellar involvement including ataxia, nystagmus, intention tremor, and dysmetria. All have short stature and most have subnormal weight. Adults have hypogonadotropic hypogonadism. Parainfectious rhabdomyolysis (profound muscle weakness, myoglobinuria, and excessively elevated serum concentration of creatine kinase usually following a viral infection) is a potentially life-threatening complication. To date all affected individuals and carriers identified have been from the Romani population.

Diagnosis/testing

The diagnosis of *CTDP1*-CCFDN is established in a proband by identification of biallelic pathogenic variants in *CTDP1* on molecular genetic testing.

Management

Treatment of manifestations: Cataracts are treated surgically; exaggerated inflammatory response and foreign-body reaction to contact lenses and intraocular lenses warrant close postoperative follow up. Peripheral neuropathy is managed symptomatically in the usual manner. Secondary spine and foot deformities may require

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surgical intervention. Developmental services and educational support as needed. Management of cerebellar manifestations per physical medicine / rehabilitation / physical and occupational therapists. Close postoperative monitoring for risk of anesthetic complications. Hormone replacement therapy for hypogonadotropic hypogonadism may help prevent osteoporosis in females. Awareness of rhabdomyolysis as a potential complication following febrile infections in order to seek medical attention with the first recognizable symptoms and to provide oral corticosteroid treatment (for 2-3 weeks for optimal recovery).

Surveillance: Annual examinations for possible ophthalmologic, neurologic, and endocrine manifestations. Developmental assessments throughout childhood.

Evaluation of relatives at risk: It is appropriate to evaluate the older and younger sibs of a proband in order to identify as early as possible those who would benefit from early initiation of treatment of ophthalmologic, neurologic, and endocrine manifestations.

Genetic counseling

CTDP1-CCFDN is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *CTDP1* 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 *CTDP1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

CTDP1-related congenital cataracts, facial dysmorphism, and neuropathy (*CTDP1*-CCFDN) **should be suspected** in individuals with the following clinical findings:

- Bilateral congenital cataracts, microcornea, and micropupils
- Mildly dysmorphic facial features apparent from late childhood (prominent midface with a well-developed nose, thickening of the perioral tissues, forwardly directed anterior dentition, and micrognathia)
- Hypo-/demyelinating peripheral neuropathy
- Mild nonprogressive intellectual deficit
- Intrauterine growth restriction with subsequent small stature and subnormal weight in adulthood

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *CTDP1*-CCFDN is **established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *CTDP1* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *CTDP1* variants of uncertain significance (or of one known *CTDP1* pathogenic variant and one *CTDP1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **targeted analysis of a pathogenic variant** and **single-gene testing**:

- **Targeted analysis** of the pathogenic variant c.863+389C>T (also known as IVS6+389C>T) can be performed first in individuals of Romani ancestry. To date, all affected individuals and carriers identified have been from the Romani population.
- **Single-gene testing.** Sequence analysis of *CTDP1* may be considered to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: (1) Although other *CTDP1* pathogenic variants may cause CCFDN, no additional variants other than c.863+389C>T have been reported to date. (2) c.863+389C>T reduces but does not abolish CTDP1 protein expression (see Molecular Genetics). It is not known if complete loss of CTDP1 results in different clinical features or is compatible with life.

Table 1. Molecular Genetic Testing Used in *CTDP1*-Related Congenital Cataracts, Facial Dysmorphism, and Neuropathy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CTDP1	Targeted analysis for c.863+389C>T [3]	100% [3, 4]
	Sequence analysis [5]	See footnote 6.
	Gene-targeted deletion/duplication analysis [7]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Romani founder variant c.863+389C>T is the only pathogenic variant reported to date.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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.
6. Sequence analysis should include detection of deep intronic variants including c.863+389C>T, the only pathogenic variant reported to date.
7. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

CTDP1-related congenital cataracts, facial dysmorphism, and neuropathy (*CTDP1*-CCFDN) is a complex disorder whose major manifestations involve the anterior segment of the eye, the skull and face, the nervous system, and the endocrine system [Tournev et al 1999a, Tournev et al 1999b, Tournev et al 2001, Merlini et al 2002, Lassuthova et al 2014, Walter et al 2014]. To date, 190 individuals have been identified with a pathogenic variant in *CTDP1* [Tournev et al 1999a, Merlini et al 2002, Müllner-Eidenböck et al 2004, Cordelli et al 2010, Lassuthova et al 2014, Walter et al 2014, Chamova et al 2015, Hudec et al 2022]. The following description of the phenotypic features associated with *CTDP1*-CCFDN is based on these reports.

Table 2. *CTDP1*-Related Congenital Cataracts, Facial Dysmorphism, and Neuropathy: Frequency of Select Features

Feature	% of Persons w/ Feature	Comment
Ocular manifestations	100%	Congenital cataracts, microcornea, microphthalmia, micropupils
Dysmorphic facial features	100%	Prominent midface w/well-developed nose, thickening of perioral tissues, forwardly directed anterior dentition, & micrognathia; more pronounced in affected males & in adulthood
Hypomyelinating peripheral neuropathy	100%	Symmetric & distally accentuated, w/predominantly motor involvement progressing to severe disability by 3rd decade of life
Developmental delay / Intellectual disability	~80%	Delayed motor milestones (attributed partly to peripheral neuropathy), delayed early intellectual development, w/most affected children starting to talk at age ~3 yrs
Cerebellar manifestations	~20%-40%	Ataxias of stance, gait, nystagmus, intention tremor, & dysmetria
Brain & spinal cord MRI abnormalities	>90%	Cerebral atrophy, thin corpus callosum, enlargement of lateral ventricles, & focal lesions in subcortical white matter (different in number & size), consistent w/ demyelination
Growth deficiency	>90%	Intrauterine growth restriction w/low weight & length at birth
Endocrine manifestations	>50%	Low levels of growth hormone & hypogonadotropic hypogonadism

Ocular Manifestations

Congenital cataracts are the invariable first manifestation of *CTDP1*-CCFDN [Tournev et al 1999a, Tournev et al 2001]. The cataracts are bilateral and can appear as anterior or posterior subcapsular opacities with clouding of the adjacent part of the lens nucleus or as total cataracts involving the entire lens [Müllner-Eidenböck et al 2004].

Other ocular manifestations include microcornea, microphthalmia (documented by axial length measurements), and micropupils with fibrotic margins, showing sluggish constriction to light and dilation to mydriatics [Müllner-Eidenböck et al 2004].

Horizontal pendular nystagmus is very common [Tournev et al 1999a, Tournev et al 2001, Müllner-Eidenböck et al 2004] and unrelated to the visual defect caused by the cataracts.

No fundus abnormalities are present.

Facial Features

Dysmorphic facial features become apparent in late childhood and are particularly evident in adult males. They include a prominent midface with a well-developed nose, thickening of the perioral tissues, forwardly directed anterior dentition, and micrognathia [Tournev et al 1999a].

Nervous System

Hypomyelinating peripheral neuropathy is symmetric and distally accentuated, with predominantly motor involvement progressing to severe disability by the third decade of life. In a study of 28 affected children ages four months to 16 years, Kalaydjieva et al [2005] observed an invariable delay in early motor development, with all starting to walk between ages two and three years, often with an unsteady gait. Clinical signs of lower-limb motor peripheral neuropathy (diminished or absent tendon reflexes, distal lower-limb weakness, and foot deformities) become apparent after age four years and are soon followed by involvement of the upper limbs [Tournev et al 1999a, Merlini et al 2002, Kalaydjieva et al 2005, Walter et al 2014].

Skeletal deformities, especially of the feet and hands (pes cavus, pes equinovarus, flexion contractures in the interphalangeal joints), develop in the course of the disease as a result of the peripheral neuropathy and are present in all affected adults. As muscle weakness progresses, spine deformities (e.g., scoliosis, kyphosis) may also develop and lead to reduction in respiratory capacity [Merlini et al 2002].

Sensory abnormalities (numbness) in the lower limbs develop in persons older than age ten years.

Nerve conduction velocity is normal in infancy at the onset of myelination and subsequently (age >18 months) begins to decline, stabilizing at approximately 20 m/s at around age four to ten years [Kalaydjieva et al 2005, Walter et al 2014]. Distal motor latencies are increased.

Sensory nerve action potentials are of normal amplitude, suggesting a relatively uniform degree of slowing of nerve conduction across nerve fibers, consistent with congenital hypomyelination. As disease progresses, reduction in amplitudes is seen in sensory and motor nerves; some (e.g., in sural nerve) can become unobtainable after age ten years, indicating secondary axonal loss [Walter et al 2014].

In distal muscles of the upper and lower extremities, neurogenic changes compatible with the underlying neuropathy are seen in all tested individuals [Tournev et al 1999b, Tournev et al 2001, Walter et al 2014]. Electromyography, performed in six individuals with proximal weakness during the rhabdomyolysis weakness episodes, showed myogenic changes in proximal muscles that were not found after recovery [Walter et al 2014].

Neuropathologic studies of sural nerve biopsies provide evidence of primary hypomyelination in the absence of morphologic abnormalities in the Schwann cell or axon [Tournev et al 1999b, Tournev et al 2001].

Central Nervous System Manifestations

Development and cognition. In addition to the delayed motor milestones (attributed partly to the peripheral neuropathy), early intellectual development is slow, with most affected children starting to talk around age three years [Tournev et al 1999b, Chamova et al 2015].

Formal assessment of cognitive ability reveals variable results, the interpretation of which should take into account visual impairment, poor educational status, and language barriers (i.e., cognitive testing performed in a language other than the individual's primary language). According to available test results, around 10% of affected individuals have normal or borderline cognitive performance, and the rest have mild nonprogressive intellectual deficit. Verbal memory, executive functions, and language skills are similarly affected [Chamova et al 2015].

Cerebellar involvement of variable severity with ataxia, nystagmus, intention tremor, and dysmetria is common [Tournev et al 1999a, Merlini et al 2002, Müllner-Eidenböck et al 2004, Lassuthova et al 2014, Walter et al 2014, Chamova et al 2015]. Ataxia scores remain stable or improve slightly during the course of the disease [Walter et al 2014].

Other neurologic manifestations

- Pyramidal signs without spasticity and extrapyramidal hyperkinesis are observed in some affected individuals [Tournev et al 2001, Chamova 2012, Chamova et al 2015].
- Individuals with *CTDP1*-CCFDN are at increased risk of developing severe and potentially life-threatening complications related to anesthesia, such as pulmonary edema, inspiratory stridor, malignant hyperthermia, and epileptic seizures [Müllner-Eidenböck et al 2004, Masters et al 2017].

Magnetic resonance imaging (MRI) findings of the brain and spinal cord vary among affected individuals and with age. Reported findings include the following:

- Cerebral, cerebellar, and cervical spine hypotrophy in childhood; cerebral atrophy with enlargement of the lateral ventricles; and occasionally thin corpus callosum and cerebellar atrophy [Tournev et al 2001, Walter et al 2014, Chamova et al 2015]
- Diffusion tensor MRI results suggestive of axonal loss in the vermis and medulla oblongata [Kalaydjieva et al 2005]
- Myelin immaturity [Tournev et al 2001]
- Multifocal white matter hyperintensity on T_2-weighted imaging; hyperintense lesions in the frontal and parietooccipital periventricular white matter and brain stem (varying from small single to multiple diffuse) [Cordelli et al 2010, Chamova 2012, Walter et al 2014, Chamova et al 2015]

Other

Growth. Intrauterine growth restriction is suggested by a study of 22 infants with *CTDP1*-CCFDN, born at term with significantly lower weight and length than in the general population [Chamova 2012]:

- **Males.** Birth weight 3.22 ± 0.48 kg (reference value 3.9 ± 0.5 kg); length 47.88 ± 3.91 cm (reference 53.1 ± 2.1 cm)
- **Females.** Birth weight 3.06 ± 0.53 kg (reference 3.8 ± 0.6 kg); length 46.75 ± 4.19 cm (reference 52.5 ± 2.1 cm)

Affected aduIts are of small stature and most are also of subnormal weight [Tournev et al 1999a]:

- **Adult males.** 149.2 ± 5 cm and 47 ± 7.2 kg (reference values: 173 ± 6.8 cm and 73.9 ± 10.4 kg)
- **Adult females.** 142.4 ± 8.2 cm and 45.8±7.6 kg (reference values: 160.3 ± 6.4 cm and 63 ± 10.7 kg)

Endocrine system. Growth hormone levels in *CTDP1*-CCFDN are in the low-normal range with a pronounced rise after insulin-induced hypoglycemia, suggesting mild regulatory deficiency [Tournev et al 1999a].

Sexual development appears unimpaired, with normal secondary characteristics after puberty and normal menarche. However, most adult females report irregular menstrual cycles and early secondary amenorrhea at ages 25-35 years.

More than half of affected adults of both sexes show evidence of hypogonadotropic hypogonadism, with low testosterone and subnormal follicle stimulating hormone levels in males and low estradiol and subnormal luteinizing hormone levels in females [Tournev et al 1999a, Tournev et al 2001, Walter et al 2014]. The impact of hypogonadotropic hypogonadism on fertility in individuals with *CTDP1*-CCFDN has not been assessed.

Bone mineral density is decreased, possibly as a result of both hypogonadotropic hypogonadism and low physical activity as a result of the peripheral neuropathy [Tournev et al 1999a, Tournev et al 2001].

Parainfectious rhabdomyolysis, a potentially life-threatening complication that leads to acute kidney failure, may in fact be an integral part of the phenotype. Rhabdomyolysis refers to disintegration of striated muscles and the release of intracellular content into the extracellular compartment, presenting clinically as profound muscle weakness, myoglobinuria, and excessively elevated serum concentration of creatine kinase. Rhabdomyolysis in *CTDP1*-CCFDN usually develops after febrile illness (mostly viral infections) and is characterized by acute severe proximal weakness and myalgia [Walter et al 2014]. Proximal muscle weakness is not otherwise typical for *CTDP1*-CCFDN [Walter et al 2014]. The episodes are usually recurrent, acute, and dramatic, but resolve spontaneously without progressing to acute renal failure [Merlini et al 2002, Mastroyianni et al 2007, Lassuthova et al 2014, Walter et al 2014]. Oral corticosteroid treatment for two to three weeks can result in a full recovery within two to six months [Walter et al 2014]. However, recovery of muscle function may take up to one year. The long-term outcome depends on the recurrence of rhabdomyolysis episodes, and such episodes can lead to deterioration in the clinical course of the peripheral neuropathy [Walter et al 2014].

Muscle biopsies have shown mild myopathic features with scattered necrotic fibers, normal histochemical reactions for myophosphorylase and phosphofructokinase, and no evidence of mitochondrial pathology [Merlini et al 2002].

Genotype-Phenotype Correlations

The *CTDP1*-CCFDN phenotype is consistent, with little variation observed among affected individuals, all of whom are homozygous for the *CTDP1* Romani founder variant c.863+389C>T.

Nomenclature

Congenital cataracts, facial dysmorphism, and neuropathy (CCFDN) was also referred to as Marinesco-Sjögren syndrome with rhabdomyolysis [Müller-Felber et al 1998] until it was demonstrated that the individuals described in that study had CCFDN [Merlini et al 2002].

The title of this *GeneReview*, *CTDP1*-related congenital cataracts, facial dysmorphism, and neuropathy (*CTDP1*-CCFDN), is based on the naming approach proposed by Biesecker et al [2021], in which mendelian disorders are designated by combining the mutated gene and resulting phenotype.

Prevalence

The prevalence of *CTDP1*-CCFDN is unknown. The total number of affected individuals diagnosed to date is approximately 190, all of Romani ancestry. The carrier rate for *CTDP1* variant c.863+389C>T is approximately 7% among the Rudari Romani and approximately 1.4% in the general Romani population [Morar et al 2004].

No affected individuals or carriers in other ethnic groups have been identified to date.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CTDP1*.

Differential Diagnosis

In early infancy, when bilateral congenital cataracts are the only manifestation, the diagnosis of *CTDP1*-related congenital cataracts, facial dysmorphism, and neuropathy (*CTDP1*-CCFDN) is made highly probable by the detection of accompanying ophthalmologic abnormalities, such as microcornea and microphthalmia.

The differential diagnosis with other conditions presenting in the first year of life with congenital cataracts, microcornea, and microphthalmia is narrowed by the delayed developmental milestones in children with *CTDP1*-CCFDN and subsequent signs of peripheral neuropathy. *CTDP1*-CCFDN also shares findings with Marinesco-Sjögren syndrome and *GBA2*-related Marinesco-Sjögren syndrome-like disorder. See Table 3.

Table 3. Disorders of Interest in the Differential Diagnosis of *CTDP1*-Related Congenital Cataracts, Facial Dysmorphism, and Neuropathy

Gene	Differential Disorder	MOI	Clinical Characteristics	Comment(s)
GALK1	Galactokinase (GALK) deficiency (OMIM 230200)	AR	Cataracts, ↑ plasma concentration of galactose, & ↑ urinary excretion of galactitol	GALK deficiency is the main differential diagnosis of *CTDP1*-CCFDN in infants of Romani ancestry. In Romani persons, GALK deficiency is caused by *GALK1* founder variant c.82C>A. [1]

Table 3. continued from previous page.

Gene	Differential Disorder	MOI	Clinical Characteristics	Comment(s)
GBA2	*GBA2*-related Marinesco-Sjögren syndrome-like disorder [2]	AR	Progressive cerebellar ataxia in early childhood accompanied by lower-limb spasticity & axonal peripheral neuropathy → weakness, muscle wasting, & foot deformities. Normal early psychomotor development; mild progressive cognitive decline accompanies other progressive CNS findings. Bilateral cataracts are observed later in disease course. [2]	Assoc w/homozygous *GBA2* variant c.1528_1529del (p.Met510ValfsTer17) [2]
INTS1	*INTS1*-related NDD (OMIM 618571)	AR	NDD w/cataracts, poor growth, & dysmorphic facies	*INTS1*-related NDD is not assoc w/peripheral neuropathy.
SIL1	Marinesco-Sjögren syndrome (MSS)	AR	Cerebellar ataxia w/cerebellar atrophy, early-onset (not necessarily congenital) cataracts, myopathy, muscle weakness, & hypotonia. Addl features may incl psychomotor delay, hypergonadotropic hypogonadism, short stature, & skeletal abnormalities. Usually presents w/muscular hypotonia in early infancy. Cataracts can develop rapidly & typically require lens extraction in 1st decade of life.	Clinical investigations providing the best distinction between *CTDP1*-CCFDN & MSS are ophthalmologic (cataracts in both disorders but extensive involvement of the anterior eye segment in *CTDP1*-CCFDN); neurophysiologic (↓ nerve conduction velocity in *CTDP1*-CCFDN); & neuroimaging (cerebellar atrophy in MSS). Electron-microscopic ultrastructural changes on muscle biopsy are thought to be specific to MSS.

AR = autosomal recessive; CNS = central nervous system; MOI = mode of inheritance; NDD = neurodevelopmental disorder
1. See Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Romani Population.
2. Haugarvoll et al [2017]

See also OMIM Phenotypic Series: Syndromic Microphthalmia and Cataract.

Management

No clinical practice guidelines for *CTDP1*-related congenital cataracts, facial dysmorphism, and neuropathy (*CTDP1*-CCFDN) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CTDP1*-CCFDN and to address the most disabling manifestations, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *CTDP1*-Related Congenital Cataracts, Facial Dysmorphism, and Neuropathy

System/Concern	Evaluation	Comment
Eyes	Ophthalmologic exam	Assess for cataracts & other ocular manifestations.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Neurologic exam incl measurements of nerve conduction velocity	Assess for peripheral neuropathy & cerebellar involvement.
	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Endocrine	Endocrinology eval	Assess growth, fertility issues, & osteopenia.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *CTDP1*-CCFDN to facilitate medical & personal decision making

ADL = activities of daily living; *CTDP1*-CCFDN = *CTDP1*-related congenital cataracts, facial dysmorphism, and neuropathy; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *CTDP1*-Related Congenital Cataracts, Facial Dysmorphism, and Neuropathy

Manifestation/Concern	Treatment	Considerations/Other
Eyes	Surgical treatment for cataract removal w/close follow up for unusually exaggerated postoperative inflammatory reactions & strong unspecific foreign-body reaction to contact lenses & intraocular lenses	• Surgical removal of cataracts may be complicated by micropupils & fibrotic pupillary margins, requiring alternative mechanical methods of dilation. [1] • Intraocular lenses are generally better tolerated than contact lenses.
Peripheral neuropathy	• Mgmt per physical medicine & rehab • Corrective surgery per orthopedics for secondary bone deformities	Consider need for positioning & mobility devices, disability parking placard.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Cerebellar manifestations	Mgmt per physical medicine & rehab / PT & OT	
Anesthesia complications	Close postoperative monitoring & possibly intensive postoperative care	For ↑ risk of severe & potentially life-threatening complications (e.g., pulmonary edema, inspiratory stridor, malignant hyperthermia, epileptic seizures) [2]
Growth deficiency	No known treatment; growth hormone levels in *CTDP1*-CCFDN are in low-normal range & growth hormone treatment is not expected to have considerable effect.	
Osteoporosis	Regular rehab	
Hypogonadotropic hypogonadism	Hormone replacement therapy may be considered in young females w/secondary amenorrhea due to ↑ risk of osteoporosis.	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Rhabdomyolysis	• Urgent assessment w/onset of any signs/ symptoms of rhabdomyolysis (e.g., muscle weakness, myoglobinuria) • Oral corticosteroid treatment for 2-3 wks can result in full recovery w/in 2-6 mos. [3]	Affected persons & care providers must be aware of risk of rhabdomyolysis, usually following febrile illness (e.g., viral infections).

CTDP1-CCFDN = *CTDP1*-related congenital cataracts, facial dysmorphism, and neuropathy; OT = occupational therapy; PT = physical therapy

1. Müllner-Eidenböck et al [2004]

2. Müllner-Eidenböck et al [2004], Hudec et al [2022]

3. Walter et al [2014]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the US; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, and speech therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the following evaluations are recommended.

Table 6. Recommended Surveillance for Individuals with *CTDP1*-Related Congenital Cataracts, Facial Dysmorphism, and Neuropathy

System/Concern	Evaluation	Frequency
Ophthalmologic involvement	Ophthalmology exam	Annually or per treating ophthalmologist(s)
Neurologic	Neurologic exam	Annually
	Orthopedics / physical medicine & rehab / PT & OT eval	As needed
Development	Monitor developmental progress & educational needs.	At each visit throughout childhood
Endocrine	Endocrine eval to assess growth, fertility issues, & osteopenia	Annually

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

General anesthesia in individuals with *CTDP1*-CCFDN may cause complications such as pulmonary edema, inspiratory stridor, malignant hyperthermia, and epileptic seizures [Müllner-Eidenböck et al 2004]. Although such complications have not been unequivocally documented, Masters et al [2017] and Hudec et al [2022] recommend cautious use of general anesthesia until more information on related risks is available.

Prolonged exercise was reported to provoke myalgia in one individual with *CTDP1*-CCFDN [Merlini et al 2002].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an affected individual in order to identify as early as possible those who would benefit from early initiation of treatment of ophthalmologic, neurologic, and endocrine manifestations.

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

Pregnancy Management

Experience is very limited, as only three females with *CTDP1*-CCFDN are known to have given birth [Tournev et al 2001, Walter et al 2014]. The pregnancies were reported as uneventful and were carried to term.

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

CTDP1-related congenital cataracts, facial dysmorphism, and neuropathy (*CTDP1*-CCFDN) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *CTDP1* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *CTDP1* pathogenic variant and to allow reliable recurrence risk assessment.
- 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 *CTDP1* 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. Unless an affected individual's reproductive partner also has *CTDP1*-CCFDN or is a carrier (which is more likely in closely knit endogamous communities with a high carrier rate; see **Family planning**), offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *CTDP1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CTDP1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *CTDP1* pathogenic variants in the family.

Because of the endogamous nature of Romani communities and the increased frequency of consanguineous marriages, carrier testing should be considered for the extended families of both parents and future reproductive partners of individuals already determined to be carriers.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- Carrier testing and genetic counseling should be offered to relatives, especially in view of the endogamous nature of many Romani communities. Even though *CTDP1*-CCFDN is a very rare disorder in the general population, the high carrier rates in specific communities (see Prevalence) translate to an increased probability of couples at high risk of having a child with *CTDP1*-CCFDN.
- 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

Once the *CTDP1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for *CTDP1*-CCFDN are possible.

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**
  Congenital cataracts, facial dysmorphism, and neuropathy
- **National Eye Institute**
  31 Center Drive
  MSC 2510
  Bethesda MD 20892-2510
  Cataracts

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. CTDP1-Related Congenital Cataracts, Facial Dysmorphism, and Neuropathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CTDP1	18q23	RNA polymerase II subunit A C-terminal domain phosphatase	CTDP1 - Leiden Muscular Dystrophy pages	CTDP1	CTDP1

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 CTDP1-Related Congenital Cataracts, Facial Dysmorphism, and Neuropathy (View All in OMIM)

604168	CONGENITAL CATARACTS, FACIAL DYSMORPHISM, AND NEUROPATHY; CCFDN
604927	C-TERMINAL DOMAIN OF RNA POLYMERASE II SUBUNIT A, PHOSPHATASE OF, SUBUNIT 1; CTDP1

Molecular Pathogenesis

The carboxy-terminal domain phosphatase 1 (CTDP1), also known as transcription factor IIF-associating CTD phosphatase 1 (FCP1), is a widely expressed nuclear protein with a catalytic N-terminal part, a phospho-protein-binding BRCT domain common to cell cycle checkpoint proteins and involved in protein-protein interactions, and a C-terminal nuclear localization signal [Archambault et al 1997, Cho et al 1999, Kobor et al 1999]. CTDP1 is involved in the regulation of eukaryotic transcription, its main function being the regulation of the phosphorylation level of the carboxy-terminal domain (CTD) of the largest subunit of RNA polymerase II (RNAPII). The CTD serves as the platform for the recruitment, assembly, and interaction of multimeric protein complexes involved in the different stages of transcription and in the post-transcriptional modifications of the nascent mRNA [Maniatis & Reed 2002]. The coupling and coordination of these processes is controlled by the changing level and pattern of phosphorylation of the serine 2 and 5 residues in the CTD, a "CTD code" that specifies the position of RNAPII in a transcription cycle [Maniatis & Reed 2002]. In vitro experiments have implicated CTDP1 in virtually all stages of the transcription cycle and multiple other processes regulating gene expression, in addition to the RNAPII recycling during transcription, such as mobilization of stored RNAPII sequestered in depots in the phosphorylated form [Palancade et al 2001], the recruitment of the splicing machinery [Licciardo et al 2003], and chromatin remodeling through histone methylation [Amente et al 2005].

Mechanism of disease causation. *CTDP1*-related congenital cataracts, facial dysmorphism, and neuropathy (*CTDP1*-CCFDN) is caused by reduced level/function of CTDP1. Some normal splicing (15%-35%) occurs in CCFDN cells; therefore, c.863+389C>T results in a partial deficiency of CTDP1 [Varon et al 2003, Kalaydjieva et al 2016].

***CTDP1*-specific laboratory technical considerations.** Alternative splicing generates two isoforms: isoform a (12 exons) is a 3,775-nucleotide transcript; isoform b (11 exons) is 3,612 nucleotides.

Table 7. Notable *CTDP1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_004715.5	c.863+389C>T [2] (IVS6+389C>T)	--	Founder variant in Romani population

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. Nucleotide change (c.863+389C>T) triggers an unusual mechanism of aberrant splicing [Varon et al 2003]. It creates a canonic donor splice site, which activates an upstream cryptic acceptor site and triggers a rare mechanism of aberrant splicing. The cryptic acceptor site is utilized together with the regular intron 6 donor site to splice out an upstream part of the intron, while the newly created donor site together with the regular intron 6 acceptor site serve for the splicing of a downstream part of the intron. An intermediate Alu sequence of 95 nucleotides is inserted into the processed *CTDP1* mRNA, resulting in a premature termination signal 17 codons downstream of exon 6.

Chapter Notes

Revision History

- 13 October 2022 (sw) Comprehensive update posted live
- 6 April 2017 (ha/bp) Comprehensive update posted live
- 2 October 2014 (me) Comprehensive update posted live
- 16 August 2012 (me) Comprehensive update posted live
- 2 March 2010 (me) Review posted live
- 29 October 2009 (lk) Original submission

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