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CTCF-Related Disorder

Synonyms: Autosomal Dominant Intellectual Disability 21, *CTCF*-Related Neurodevelopmental Disorder

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Summary

Clinical characteristics

CTCF-related disorder is characterized by developmental delay / intellectual disability (ranging from mild to severe), with both speech and motor delays being common; feeding difficulties, including dysphagia, and other gastrointestinal issues (gastroesophageal reflux disease and/or irritable bowel syndrome) that can lead to growth deficiency; hypotonia; eye anomalies (strabismus and/or refractive errors); scoliosis; nonspecific dysmorphic features; sleep disturbance; tooth anomalies (crowded teeth and/or abnormal decay); and, less commonly, other congenital anomalies (cleft palate, gastrointestinal malrotation, genitourinary anomalies, and congenital heart defects, including aortic ectasia). Short stature, seizures, hearing loss, recurrent infections, microcephaly, and autistic features have also been described in a minority of affected individuals. At least four reported individuals with *CTCF*-related disorder developed Wilms tumor, one of whom had bilateral Wilms tumor. However, there is no clear evidence of a significant predisposition for the development of cancer in individuals with *CTCF*-related disorder at this time.

Diagnosis/testing

The diagnosis of *CTCF*-related disorder is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *CTCF* identified by molecular genetic testing.

Management

Treatment of manifestations: Feeding therapy with a low threshold for clinical feeding evaluation and/or radiographic swallowing study for those with clinical signs or symptoms of dysphagia; gastrostomy tube placement may be required for persistent feeding issues. Stool softeners, prokinetics, osmotic agents, or laxatives as needed for constipation. Conductive hearing loss may respond to placement of PET; hearing aids may be

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helpful per otolaryngologist. Standard treatment for developmental delay / intellectual disability, neurobehavioral issues, gastroesophageal reflux disease, strabismus, refractive errors, ptosis, cleft palate, dental anomalies, scoliosis, hip dysplasia, ankle/foot anomalies, sleep disturbance, recurrent infections, renal anomalies, anomalies of the genitalia, congenital heart defects, seizures, and Wilms tumor.

Surveillance: At each visit: measure growth parameters and evaluate nutritional status and safety of oral intake; monitor for gastroesophageal reflux disease and/or constipation; assess for new manifestations such as seizures or changes in tone; monitor developmental progress and educational needs; assess for behavioral issues or changes in behavior; monitor for signs/symptoms of sleep disturbance; assess for frequent infections. Assess for signs and symptoms of scoliosis at least annually until skeletal maturity. Dental and ophthalmology evaluations at least annually or as clinically indicated. Annual audiology evaluation through childhood or as clinically indicated. No tumor screening protocol for individuals with *CTCF*-related disorder has been developed.

Pregnancy management: In general, women with epilepsy or a seizure disorder of any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication (ASM) during pregnancy reduces this risk. However, exposure to ASMs may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to or during pregnancy may be possible.

Genetic counseling

CTCF-related disorder is inherited in an autosomal dominant manner. Approximately 80% of individuals with *CTCF*-related disorder whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo CTCF* pathogenic variant. If a parent of the proband is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Once the *CTCF* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *CTCF*-related disorder have been published.

Suggestive Findings

CTCF-related disorder **should be considered** in probands with the following clinical findings and family history.

Clinical findings

- Mild-to-profound developmental delay (DD) or intellectual disability (ID)

AND

- Any of the following features presenting in infancy or childhood:
  - Hypotonia
  - Feeding difficulties
  - Slow growth
  - Neurobehavioral/psychiatric manifestations, including autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), aggression, anxiety, and/or destructive behaviors
  - Ophthalmologic involvement, including strabismus, hypermetropia, astigmatism, amblyopia, and/or myopia
  - Sensorineural or conductive hearing loss
  - Nonspecific dysmorphic features (See Clinical Description.)

- Cleft palate
- Congenital heart defects
- Tooth anomalies, such as crowded teeth and abnormal decay
- Genitourinary anomalies
- Sleep disturbance
- Recurrent infections
- Seizures

Family history. Because *CTCF*-related disorder is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of *CTCF*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *CTCF* identified by molecular genetic testing (see Table 1).

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

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with exome sequencing / genome sequencing [Manickam et al 2021, van der Sanden et al 2023]. Other options include use of chromosomal microarray analysis (CMA) or a multigene panel. Note: Single-gene testing (sequence analysis of *CTCF*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An intellectual disability multigene panel** that includes *CTCF* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA 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*. Of note, given the rarity of *CTCF*-related disorder, some panels for intellectual disability may not include this gene. (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.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an intellectual disability multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability, whereas some multigene panels may not. To date, the majority of *CTCF* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing.

  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.

Table 1. Molecular Genetic Testing Used in *CTCF*-Related Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
CTCF	Sequence analysis [3]	~92% [4]
	CMA [5]	~8% [4]
	Gene-targeted deletion/duplication analysis [6]	Additional percentage detected by this method unknown [7]

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. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Valverde de Morales et al [2023]
5. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use target the 16q22.1 region.
6. 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.
7. Theoretically, gene-targeted deletion/duplication analysis should detect all deletions/duplications that can be detected by CMA. However, CMA may not detect all instances of single- or several-exon deletions or duplications depending on the probe coverage through various parts of a gene.

Clinical Characteristics

Clinical Description

To date, more than 100 individuals have been identified with a pathogenic variant in *CTCF* [Valverde de Morales et al 2023].

Table 2. Select Features of *CTCF*-Related Disorder

Feature	% of Persons w/Feature	Comment
Developmental delay / intellectual disability	91%	Both speech & motor delays have been described.
Feeding difficulties / growth problems	66%	Most typically poor growth in infancy
Eye anomalies	56%	Most commonly strabismus or refractive errors
Musculoskeletal anomalies	53%	Most commonly scoliosis
Behavioral issues	52%	
Hypotonia	45%	Which may contribute to motor delay & feeding difficulties
Tooth anomalies	39%	Most typically crowded teeth & abnormal decay
Sleep disturbance	34%	
Gastrointestinal issues	34%	Incl constipation &/or GERD
ASD or autistic features	31%	
Low weight	29%	
Microcephaly	26%	
Recurrent infections	~26%	No primary immune deficiency in affected persons has been reported, although 1 person had low IgA levels. [1]

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Palatal anomalies	25%	
Genitourinary anomalies	25%	
Hearing loss	24%	Both sensorineural & conductive hearing loss have been reported.
Short stature	23%	
Congenital heart defects	22%	
Seizures	18%	No consistent type has been reported.

Adapted from Valverde de Morales et al [2023]
ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; IgA = immunoglobulin A
1. H Li, personal observation

Developmental delay (DD) and intellectual disability (ID). The vast majority of affected individuals have developmental delay and intellectual disability, ranging from mild to severe.

- About 65% of affected individuals have been reported to have speech delay, ranging from mild delay to individuals who are nonverbal. The mean age of saying the first word is 20 months, with a range of 10 months to 5 years.
- About 53% of affected individuals have been reported as having motor delay, with 10/42 (24%) of reported individuals having coordination or balance issues.
    - Mean age of sitting without support is 12 months, with a range from 6 months to 24 months.
    - Mean age of walking independently is 18 months, with a range from 12 months to 42 months.
    - At least one affected individual was nonambulatory at age 17 years.

Neurobehavioral/psychiatric manifestations. The most common neurobehavioral manifestations are autism spectrum disorder / autistic features and attention-deficit/hyperactivity disorder, although most affected individuals do not have either of these findings. Less frequent behavioral/psychiatric manifestations may include:

- Aggression
- Anxiety
- Difficulty regulating emotions
- Destructive behaviors
- Oppositional behaviors
- Self-injurious behaviors

Hypotonia has been described in just under half of affected individuals. Hypotonia may contribute to both motor and feeding issues.

Gastrointestinal/feeding. Infant feeding difficulties are common. Contributing factors may include dysphagia, cleft palate, and hypotonia. A minority of affected individuals have required placement of a feeding tube (see Management).

- Feeding problems are most commonly reported in early infancy, with some individuals experiencing resolution of feeding problems at older ages, most with the removal of their feeding tube.
- About 17% of affected individuals experience constipation.
- Other reported functional gastrointestinal complications include gastroesophageal reflux disease, dysphagia, and irritable bowel syndrome.
- Gastrointestinal malformations may include intestinal malrotation and rectal duplication.

Growth. In affected individuals, weight is the most consistently impacted growth parameter, with about 29% of affected individuals demonstrating low weight (2 standard deviations below the mean for age and sex). In initial publications [Gregor et al 2013], microcephaly and short stature were listed as characteristic features of individuals with *CTCF*-related disorder; however, only about one fourth of affected individuals have short stature (24/102) and/or microcephaly (27/102).

Facial features. No consistent dysmorphic features have been observed across described individuals with *CTCF*-related disorder to suggest a recognizable facial phenotype. If present, dysmorphic features are nonspecific. Individuals with *CTCF*-related disorder can commonly demonstrate widely spaced and/or deep-set eyes, broad nasal bridge, broad nasal tip, and thin vermilion of the upper lip.

Ophthalmologic involvement. Strabismus or refractive errors were found in more than half of individuals. While strabismus is the most commonly reported issue, other reported problems include:

- Hypermetropia
- Astigmatism
- Amblyopia
- Myopia
- Ptosis

Hearing impairment has also been reported in affected individuals. Both unilateral and bilateral hearing loss have been reported. Hearing loss may also be sensorineural and/or conductive in nature. Many reported individuals with *CTCF*-related disorder who have hearing loss have benefited from the use of hearing aids (see Management).

Craniofacial/dental. About one quarter of affected individuals have been reported to have a cleft palate, and about one third of affected individuals have been found to have dental anomalies unrelated to cleft palate. Other reported dental issues include:

- Impacted teeth
- Increased incidence of dental decay
- Ectopic teeth
- Absent secondary teeth
- Abnormal shape of teeth
- Discoloration of teeth
- Midline misalignment

Musculoskeletal features have been reported in approximately half of affected individuals. Scoliosis is the most common finding and tends to be static. Less common findings include:

- Kyphosis
- Vertebral compression fractures, most typically in older individuals
- Hip dysplasia
- Pes valgus
- Bilateral clubfeet
- Genu valgum
- Calcaneus valgus
- Tight tendons requiring tenotomies
- Finger abnormalities, such as camptodactyly

Sleep disturbance. About one third of affected individuals have been reported to have issues with sleep. In some affected individuals this may manifest as delayed sleep onset (difficulty falling asleep), while in others it can

present as frequent awakenings. Some affected individuals have benefited from pharmacologic therapy, including melatonin or clonidine (see Management).

Recurrent infections. To date, 27 individuals with *CTCF*-related disorder have been reported to have recurrent infections [Gargallo et al 2022, Valverde de Morales et al 2023]. Recurrent respiratory infections, urinary tract infections, otitis media, and impetigo are some of the most commonly reported findings. One affected individual has low IgA levels [H Li, personal observation].

Genitourinary abnormalities have been documented in about one quarter of reported individuals. While renal anomalies were reported in both males and females, anomalies of the genitalia were most often reported in males [Gargallo et al 2022, Valverde de Morales et al 2023].

- Renal findings include:
  - Dysplastic kidney
  - Solitary kidney
  - Polycystic kidney
  - Renal ectasia
  - Vesicoureteral reflux disease
  - Renal insufficiency, typically not as a primary finding but secondary to renal anomalies or history of Wilms tumor
- Anomalies of the genitalia in males can include:
  - Cryptorchidism
  - Spermatocele
  - Penile chordee
  - Phimosis
  - Hypospadias
- In females, hypoplastic labia majora has been noted.

Cardiac findings. Congenital heart defects were reported in 22 affected individuals. Reported findings include [Gargallo et al 2022, Valverde de Morales et al 2023]:

- Atrial septal defects
- Tetralogy of Fallot
- Pulmonary valve stenosis
- Patent ductus arteriosus
- Mild aortic coarctation
- Aortic ectasia (Aortic rupture has not been reported to date in individuals with this condition, although data on progression of this finding is limited.)
- Bicuspid aortic valve

Seizures are a less common finding in affected individuals, with fewer than 20% experiencing seizures. In those who do have seizures, there is no consistent seizure type. Similarly, there is no consistent age of onset for seizures, with onset ranging from early infancy to primary school age (age ~6 years) to adolescence (one individual had initial seizure at age 15 years). Reported seizure types include:

- Febrile seizures
- Generalized tonic-clonic seizures
- Tonic seizures
- Petit mal seizures

Neuroimaging. Brain MRI has been normal in most affected individuals who have undergone imaging; however, some individuals have nonspecific findings, such as white matter abnormalities, gray matter

heterotopia, focal polymicrogyria, periventricular leukomalacia, focal simplified gyration, thin corpus callosum, and prominent lateral ventricles. One affected individual was reported to have mild but progressive cerebellar and cerebral atrophy [Valverde de Morales et al 2023].

Malignancy. At least four reported individuals with *CTCF*-related disorder developed Wilms tumor, with ages at diagnosis being one, two, four, and five years, respectively. One affected individual had bilateral Wilms tumor [Konrad et al 2019, Gargallo et al 2022, Valverde de Morales et al 2023]. However, there is no clear evidence of a significant predisposition for the development of cancer in individuals with *CTCF*-related disorder at this time. Therefore, no tumor screening protocol for individuals with *CTCF*-related disorder has been developed.

Prognosis. It is unknown whether life span in *CTCF*-related disorder is abnormal. More than 16 adult individuals with *CTCF*-related disorder have been reported in the literature, with the oldest individual being age 34 years at the time of the report [Valverde de Morales et al 2023], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No consistent genotype-phenotype correlations have been identified [Valverde de Morales et al 2023].

Prevalence

CTCF-related disorder is a rare disorder. Though the prevalence is unknown, 107 individuals from different countries (Canada, China, Denmark, England, France, Israel, Italy, Japan, Norway, Spain, United Arab Emirates, and United States) have been reported in the literature [Gargallo et al 2022, Temple et al 2022, Chen et al 2023, Lyu et al 2023, Valverde de Morales et al 2023]. As most reported affected individuals have been diagnosed recently using whole exome sequencing, this condition is likely underdiagnosed and underreported.

Genetically Related (Allelic) Disorders

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

Sporadic tumors (including endometrial, head and neck, and breast cancer) occurring as single tumors in the absence of any other findings of *CTCF*-related disorder often contain a somatic pathogenic variant in *CTCF* that is not present in the germline [Valverde de Morales et al 2023]. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

The phenotypic features associated with *CTCF*-related disorder are not sufficient to diagnose this condition clinically; therefore, all conditions in which affected individuals have developmental delay and/or intellectual disability without other distinctive findings should be considered in the differential diagnosis, especially if the condition is also associated with feeding difficulties and growth deficiency.

See OMIM Phenotypic Series for genes associated with:

- Autosomal dominant intellectual developmental disorder
- Autosomal recessive intellectual developmental disorder
- Nonsyndromic X-linked intellectual developmental disorders
- Syndromic X-linked intellectual developmental disorders

Management

No clinical practice guidelines for *CTCF*-related disorder have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CTCF*-related disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. *CTCF*-Related Disorder: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To assess for poor growth, short stature, & microcephaly
Craniofacial	Assessment for palatal anomalies &/or dental anomalies	Consider referral to a craniofacial clinic.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk, nutritional status, GERD, & constipation • Consider eval for feeding therapy or gastrostomy tube placement in affected persons w/dysphagia &/or aspiration risk. • Assess for intestinal malrotation & GI anomalies prior to gastrostomy tube placement.
Neurologic	Neurologic eval	• To incl brain MRI as clinically indicated • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Eyes	Ophthalmologic eval	To assess for strabismus, ptosis, or refractive errors
Hearing	Audiologic eval	To assess for hearing loss
Musculoskeletal	Clinical assessment for scoliosis, hip dysplasia, & ankle or foot anomalies	Consider spinal radiographs &/or referral to orthopedist.
	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)
Sleep	Assessment for signs & symptoms of sleep disturbance	Consider referral to a sleep disorders specialist.
Immunologic	Assessment for history of recurrent infections	• Consider referral to appropriate specialist (pulmonologist if respiratory concerns, ENT if recurrent otitis media, dermatologist if impetigo is present, or nephrologist if there are multiple urinary tract infections). • Consider referral to immunologist if recurrent, severe infections are present.
Genitourinary	Assessment for genital anomalies, incl cryptorchidism & hypospadias in males	Consider referral to urologist.
	Renal ultrasound	To evaluate for renal anomalies & hydronephrosis

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Cardiovascular	Echocardiogram	To evaluate for structural heart defects & aortic ectasia
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *CTCF*-related disorder to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; ENT = ear, nose, and throat specialist (otolaryngologist); GERD = gastroesophageal reflux disease; GI = gastrointestinal; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *CTCF*-related disorder. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. *CTCF*-Related Disorder: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Gastroesophageal reflux disease	Standard therapy per gastroenterologist	
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Strabismus, refractive errors, & ptosis	Standard treatment per ophthalmologist	
Hearing loss	• Conductive hearing loss may respond to placement of PET. • Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district as clinically indicated
Cleft palate / Dental anomalies	Standard treatment per craniofacial team, ENT, &/or dentist	
Scoliosis, hip dysplasia, or ankle/foot anomalies	Standard treatment per orthopedist	
Sleep disturbance	Standard treatment per sleep disorder specialist	This may incl improving sleep hygiene &/or pharmacologic therapy such as melatonin or clonidine

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Recurrent infections	Standard treatment per the appropriate specialist	E.g., pulmonologist if respiratory concerns, ENT if recurrent otitis media, dermatologist if impetigo is present, or nephrologist if there are multiple urinary tract infections
Renal anomalies	Standard treatment per urologist &/or nephrologist	
Anomalies of genitalia	Standard treatment per urologist or gynecologist	
Congenital heart defects	Standard treatment per cardiologist	
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • 1 affected person responded well to a sodium channel blocker. [1] • Education of parents/caregivers [2]
Wilms tumor	Standard treatment per oncologist	It is unclear if persons w/*CTCF*-related disorder are at increased risk above general population of developing Wilms tumor.
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for home nursing • Consider involvement in adaptive sports or Special Olympics.

Adapted from Valverde de Morales et al [2023]
ASM = anti-seizure medication; ENT = ears, nose, and throat specialist (otolaryngologist); OT = occupational therapy; PET = pressure-equalizing tubes; PT = physical therapy
1. H Li, personal observation
2. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; 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, speech, and feeding 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, social, 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 and hearing 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).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

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.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. *CTCF*-Related Disorder: Recommended Surveillance

System/Concern	Evaluation	Frequency
Growth/Feeding	• Measure growth parameters. • Evaluate nutrition status & safety of oral intake.	At each visit
Gastrointestinal	Monitor for GERD &/or constipation.	
Neurologic	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations such as seizures or changes in tone.	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Assess for anxiety, ADHD, ASD, aggression, & self-injury.	
Sleep	Monitor for signs & symptoms of sleep disturbance.	
Immunologic	Assess for frequent infections.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
	Assess for signs & symptoms of scoliosis.	At each visit until skeletal maturity
Cardiovascular	Standard follow up w/cardiologist if anomalies are detected. [1]	As clinically indicated
Dental	Dental eval	At least annually or as clinically indicated
Eyes	Ophthalmology eval	At least annually or as clinically indicated
Hearing	Audiology eval	At least annually through childhood or as clinically indicated

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Family/Community	Assess family need for social work support (e.g., home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit
Malignancy	No tumor screening protocols have been developed or recommended at this time. [2]	NA

Adapted from Valverde de Morales et al [2023]
ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; GERD = gastroesophageal reflux disease; NA = not applicable; OT = occupational therapy; PT = physical therapy
1. Two individuals have been reported with mild aortic dilatation, both of whom were age ten years or younger at the time and both of whom had other cardiovascular findings (bicuspid aortic valve or pulmonary valve stenosis). It is unclear if individuals with *CTCF*-related disorder are at risk of progressive aortic dilatation.
2. It is unclear if individuals with *CTCF*-related disorder are at increased risk above the general population of developing Wilms tumor or any other malignancy. Though no specific guidelines for surveillance for Wilms tumor have been proposed, providers may consider educating families on the symptoms/signs of Wilms tumor.

Evaluation of Relatives at Risk

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

Pregnancy Management

Limited data is available on pregnancies for women with *CTCF*-related disorder.

In general, women with epilepsy or a seizure disorder of any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication (ASM) during pregnancy reduces this risk. However, exposure to ASMs may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from ASM exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of ASMs to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to or during pregnancy may be possible [Sarma et al 2016].

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

CTCF-related disorder is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 80% of individuals with *CTCF*-related disorder whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo CTCF* pathogenic variant [Valverde de Morales et al 2023].
- To date, nine individuals diagnosed with *CTCF*-related disorder inherited a *CTCF* pathogenic variant from a typically asymptomatic parent. Two of the transmitting parents were mosaic for the detected pathogenic variants [Valverde de Morales et al 2023].
- Molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with *CTCF*-related disorder may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance in a heterozygous parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *CTCF* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Valverde de Morales et al 2023].
- If the parents have not been tested for the *CTCF* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *CTCF*-related disorder because of the possibility of reduced penetrance in a heterozygous parent or the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *CTCF*-related disorder has a 50% chance of inheriting the *CTCF* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *CTCF* pathogenic variant, the parent's family members may be at risk.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CTCF* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing 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.

- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **MedlinePlus**
  Intellectual Disability

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. CTCF-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
CTCF	16q22.1	Transcriptional repressor CTCF	CTCF	CTCF

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 CTCF-Related Disorder (View All in OMIM)

604167	CCCTC-BINDING FACTOR; CTCF
615502	INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL DOMINANT 21; MRD21

Molecular Pathogenesis

Transcriptional repressor CTCF (CTCF; also called CCCTC-binding factor) is a DNA-binding transcription factor that plays a critical role in regulating gene expression and chromatin organization [Phillips & Corces 2009]. CTCF contains 727 amino acids and three functional domains: an N-terminal domain (residues 1-267), a central DNA-binding domain with 11 tandem Cys2-His2 (C2H2) zinc fingers (ZFs) (residues 268-577), and a C-terminal domain (residues 578-727). The ZFs largely orchestrate the interaction between CTCF and specific DNA sequences that are found throughout the genome. The RNA-binding domain (RBD) of CTCF interacts with RNA as well. CTCF can function as a transcriptional activator or repressor, depending on its binding location and iterating partners. CTCF organizes the three-dimensional structure of the genome by forming DNA

loops and facilitating the formation of higher-order chromatin structures for proper cellular function and development. In addition to its role in chromatin organization, CTCF is involved in genomic imprinting, DNA methylation patterning, X-chromosome inactivation, and alternative splicing [Kung et al 2015, Hashimoto et al 2017, Hansen et al 2019, Saldaña-Meyer et al 2019, Alharbi et al 2021].

Missense pathogenic variants account for more than half of reported pathogenic variants. The majority of pathogenic missense variants are located in ZFs, particularly in the DNA-binding region and less commonly in other functional domains, such as the RBD and Tyr-Asp-Phe (YDF) domains [Valverde de Morales et al 2023].

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

The Emory *CTCF*-related disorder center (www.ctcfemory.com), led by Dr Hong Li and Dr Victor Corces, is devoted to understanding the phenotypic spectrum, natural history, and molecular mechanism of *CTCF*-related disorder. For information about ongoing research studies, contact ctcf@emory.edu·

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