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Cockayne Syndrome

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Summary

Clinical characteristics

Cockayne syndrome (referred to as CS in this *GeneReview*) spans a continuous phenotypic spectrum that includes:

- CS type I, the "classic" or "moderate" form;
- CS type II, a more severe form with symptoms present at birth; this form overlaps with cerebrooculofacioskeletal (COFS) syndrome;
- CS type III, a milder and later-onset form;
- COFS syndrome, a fetal form of CS.

CS type I is characterized by normal prenatal growth with the onset of growth and developmental abnormalities in the first two years. By the time the disease has become fully manifest, height, weight, and head circumference are far below the fifth percentile. Progressive impairment of vision, hearing, and central and peripheral nervous system function leads to severe disability; death typically occurs in the first or second decade.

CS type II is characterized by growth failure at birth, with little or no postnatal neurologic development. Congenital cataracts or other structural anomalies of the eye may be present. Affected children have early postnatal contractures of the spine (kyphosis, scoliosis) and joints. Death usually occurs by age five years.

CS type III is a phenotype in which major clinical features associated with CS only become apparent after age two years; growth and/or cognition exceeds the expectations for CS type I.

COFS syndrome is characterized by very severe prenatal developmental anomalies (arthrogryposis and microphthalmia).

Diagnosis/testing

The diagnosis of Cockayne syndrome is established in a proband with the identification of biallelic pathogenic variants in *ERCC6* or *ERCC8* on molecular genetic testing.

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Management

Treatment of manifestations: Feeding gastrostomy tube placement as needed; individualized educational programs for developmental delay; medications for tremor and spasticity as needed; physical therapy to prevent contractures; use of sunglasses for lens/retina protection; treatment of cataracts, and other ophthalmologic complications, hearing loss, hypertension, and gastroesophageal reflux as in the general population. Aggressive dental care to minimize dental caries; use of sunscreens and limitation of sun exposure for cutaneous photosensitivity.

Surveillance: Biannual assessment of diet, nervous system, and ophthalmologic status. Yearly assessment for complications such as hearing loss, hepatic or renal dysfunction, and hypertension.

Agents/circumstances to avoid: Excessive sun exposure and use of metronidazole. Extra vigilance is needed for opioid and sedative use. Use of growth hormone treatment is not recommended in those with CS.

Genetic counseling

Cockayne syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic diagnosis are possible if the *ERCC6* or *ERCC8* pathogenic variants in the family are known.

GeneReview Scope

Cockayne Syndrome (CS): Included Phenotypes
• CS type I • CS type II • CS type III • Cerebrooculofacioskeletal (COFS) syndrome

For synonyms and outdated names see Nomenclature.

Diagnosis

Cockayne syndrome (CS) is characterized by growth failure and multisystemic involvement, with a variable age of onset and rate of progression. To facilitate clinical recognition and follow up, the phenotypic spectrum of CS can be divided into different clinical presentations. Note, however, that among all individuals with CS there is a continuous spectrum of clinical severities without clear thresholds and that intermediate phenotypes may arise:

- **Cockayne syndrome type I,** "classic" CS, in which the major features of the disease become apparent by age one to two years
- **Cockayne syndrome type II,** a more severe form with abnormalities recognized at birth or in the early neonatal period
- **Cockayne syndrome type III,** milder/later-onset forms in which major features only become apparent after age two years
- **Cerebrooculofacioskeletal (COFS) syndrome,** very severe fetal phenotype with arthrogryposis, prenatal growth failure, prenatal microcephaly, congenital cataracts or microphthalmia

Formal clinical diagnostic criteria originally proposed for CS type I [Nance & Berry 1992] have been revised and extended in more recent publications [Natale 2011, Laugel 2013]. Because of the progressive nature of CS, the clinical diagnosis becomes more certain as additional signs and symptoms gradually manifest over time.

Suggestive Findings

Cockayne syndrome **should be suspected** in individuals with the following findings.

Major criteria

- Postnatal growth failure (height and weight <5th centile by age 2 years)
- Progressive microcephaly and neurologic dysfunction manifested as early developmental delay in most individuals, followed by progressive behavioral and intellectual deterioration in all individuals; brain MRI reveals white matter dysmyelination and cerebellar atrophy [Koob et al 2010, Koob et al 2016]. Intracranial calcifications (mainly located in the basal ganglia) are seen in some individuals.

Minor criteria

- Cutaneous photosensitivity
- Demyelinating peripheral neuropathy diagnosed by nerve conduction testing
- Pigmentary retinopathy and/or cataracts
- Sensorineural hearing loss
- Dental anomalies including dental caries, enamel hypoplasia, and anomalies of tooth number and tooth size and shape
- A characteristic physical appearance of "cachectic dwarfism" with sunken eyes

CS type I (classic) is suspected:

- In an older child when both major criteria are present and three minor criteria are present;
- In an infant or toddler when both major criteria are present, especially if there is increased cutaneous photosensitivity.

CS type II (severe) is suspected:

- In infants with growth failure at birth and little postnatal increase in height, weight, or head circumference;
- When there is little or no postnatal neurologic development;
- When congenital cataracts are present.

CS Type III (mild) is suspected:

- In children or teenagers with short stature, mild neurologic impairment, and progressive ataxia;
- Especially but not exclusively when there is cutaneous photosensitivity.

COFS syndrome is suspected when prenatal growth failure and prenatal microcephaly are associated with arthrogryposis and congenital cataracts as well as other structural defects of the eye (microphthalmos, microcornea, iris hypoplasia).

Establishing the Diagnosis

The diagnosis of Cockayne syndrome **is established** in a proband by identification of biallelic pathogenic variants in *ERCC6* or *ERCC8* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, 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. Because the phenotype of Cockayne syndrome is broad, 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 Cockayne syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of Cockayne syndrome the recommended molecular genetic testing approach is to use a **multigene panel**.

A multigene panel that includes *ERCC6*, *ERCC8*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the diagnosis of Cockayne syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 Cockayne Syndrome

Gene [1, 2]	Proportion of Cockayne Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ERCC6	~65%	90%[6]	10% [6]

Table 1. continued from previous page.

Gene [1, 2]	Proportion of Cockayne Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
ERCC8	~35%	88% [6]	12% [6]

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 allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. Laugel et al [2010], Calmels et al [2018]

DNA Repair Assay

If the diagnosis of Cockayne syndrome is strongly suspected, but the molecular genetic testing does not identify pathogenic variants in one of the associated genes, an assay of the cellular phenotype can be considered.

Assays of DNA repair are performed on skin fibroblasts. The most consistent findings in CS fibroblasts are marked sensitivity to UV radiation and deficient recovery of RNA synthesis following UV damage (i.e., impaired repair of actively transcribed genes, or "transcription-coupled repair") [Nakazawa et al 2010].

Clinical Characteristics

Clinical Description

Before the molecular genetics of Cockayne syndrome was understood, it was thought to have a single, discrete phenotype: classic Cockayne syndrome. It is now recognized that Cockayne syndrome spans a continuous phenotypic spectrum without clear thresholds, and includes the following [Nance & Berry 1992]:

- CS type I, the "classic" form
- CS type II, a more severe form with symptoms present at birth (overlapping with cerebrooculofacioskeletal syndrome [COFS])
- CS type III, a milder form
- Cerebrooculofacioskeletal (COFS) syndrome, the most severe end of the phenotypic spectrum of CS with findings identifiable during fetal life

CS Type I

Presentation. Prenatal growth is typically normal. Birth length, weight, and head circumference are normal. Within the first two years, however, growth and development fall below normal. By the time the disease has become fully manifest, height, weight, and head circumference are far below the fifth percentile.

Progression. Progressive impairment of vision, hearing, and central and peripheral nervous system function leads to severe disability. Brain MRI reveals white matter dysmyelination and progressive cerebral and cerebellar atrophy. Photosensitivity is variable, but individuals are not predisposed to skin cancers.

Additional clinical abnormalities occurring in 10% or more of individuals include the following:

- **Neurologic.** Increased tone/spasticity, hyper- or hyporeflexia, stooped standing posture, abnormal gait or inability to walk, ataxia, incontinence, tremor, abnormal or absent speech, seizures, weak cry / poor feeding (as an infant), muscle atrophy, and behavior abnormality
- **Dermatologic.** Anhidrosis, malar rash, thin dry hair [Frouin et al 2013]
- **Ophthalmologic.** Enophthalmos, pigmentary retinopathy (60%-100%), abnormal electroretinogram, cataracts of various types (15%-36%), optic atrophy, miotic pupils, farsightedness, decreased or absent tears, strabismus, nystagmus, photophobia, narrowed retinal arterioles
- **Hearing**. Sensorineural hearing loss
- **Dental.** Absent or hypoplastic teeth, enamel hypoplasia, delayed eruption of deciduous teeth, and malocclusion. Enamel anomalies frequently lead to severe dental caries [Bloch-Zupan et al 2013].
- **Skeletal.** Radiographic findings of thickened calvarium (due to microcephaly), sclerotic epiphyses, vertebral and pelvic abnormalities
- **Renal.** Abnormal renal function, proteinuria, nephrotic syndrome, hyperuricemia, hypertension [Stern-Delfils et al 2019]
- **Endocrine.** Undescended testes, delayed/absent sexual maturation, diabetes
- **Gastrointestinal.** Elevated liver function tests, enlargement of liver or spleen, gastroesophageal reflux

Death typically occurs in the first or second decade. The mean age of death is 16 years, although survival into the third decade has been reported [Natale 2011].

CS Type II

Children with severe CS have evidence of growth failure at birth, with little or no postnatal neurologic development. Congenital cataracts or other structural anomalies of the eye are present in 30%. Affected individuals may have some contractures of the spine (kyphosis, scoliosis) and joints in neonatal or early postnatal life. Affected children typically die by age five years [Natale 2011]. CS type II partly overlaps with cerebrooculofacioskeletal (COFS) syndrome.

CS Type III

DNA sequencing has confirmed the diagnosis of CS type III in some individuals who have clinical features associated with CS but whose growth and/or cognition exceeds the expectations for CS type I [Natale 2011, Baez et al 2013]. Major features only become apparent after age two years.

COFS Syndrome

COFS syndrome is the most severe subtype of the CS spectrum and can be identified during fetal life. Similarly to individuals with CS type II, individuals with COFS syndrome present with severe prenatal growth failure, severe developmental delay / intellectual disability from birth, axial hypotonia, peripheral hypertonia, and neonatal feeding difficulties. COFS syndrome is additionally defined by the presence of arthrogryposis and usually the combination of extreme congenital microcephaly and congenital cataracts [Laugel et al 2008].

Neuropathology. In all forms of Cockayne syndrome, a characteristic "tigroid" pattern of demyelination in the subcortical white matter of the brain and multifocal calcium deposition, with relative preservation of neurons and without senile plaques, amyloid, ubiquitin, or tau deposition, has been observed together with arteriosclerosis [Weidenheim et al 2009, Hayashi et al 2012].

Genotype-Phenotype Correlations

To date no genotype-phenotype correlations for *ERCC6* or *ERCC8* have been clearly identified.

Nomenclature

The term cerebrooculofacioskeletal (COFS) syndrome and its former synonym, Pena-Shokeir syndrome type II, have been used to refer to a heterogeneous group of disorders characterized by congenital neurogenic arthrogryposis (multiple joint contractures), microcephaly, microphthalmia, and cataracts. The original cases of COFS syndrome, described by Pena & Shokeir [1974] among native Canadian families from Manitoba, have since been shown to be homozygous for a pathogenic variant in *ERCC6*. COFS syndrome is now regarded as an allelic and prenatal form of CS, partly overlapping with CS type II and including the most severe cases of the CS phenotypic spectrum [Laugel et al 2008].

Prevalence

The minimum incidence of CS has been estimated at 2.7 per million births in western Europe; the disease is probably underdiagnosed [Kleijer et al 2008].

Genetically Related (Allelic) Disorders

Other phenotypes associated with germline pathogenic variants in *ERCC6* and *ERCC8* are summarized in Table 2.

Table 2. Allelic Disorders

Gene	Disorder	Reference
ERCC6	UV-sensitive syndrome 1	Horibata et al [2004]
	Premature ovarian failure (reported in 1 study)	Qin et al [2015]
ERCC8	UV-sensitive syndrome 2	Nardo et al [2009]

Differential Diagnosis

The differential diagnosis of Cockayne syndrome (CS) depends on the presenting features of the particular individual (see Table 3). Abnormalities that suggest alternative diagnoses include: congenital anomalies of the face, limbs, heart, or viscera; recurrent infections (other than otitis media or respiratory infections); metabolic or neurologic crises; hematologic abnormality (e.g., anemia, leukopenia); and cancer of any kind.

Growth failure is seen in chromosome disorders and endocrine, metabolic, or gastrointestinal disorders, including malnutrition.

Table 3. Disorders to Consider in the Differential Diagnosis of Cockayne Syndrome

Disorder	Gene(s)	MOI	Clinical Features of Cockayne Syndrome	
			Also in differential diagnosis disorder	Not in differential diagnosis disorder
Connatal form of Pelizaeus-Merzbacher disease [1]	*PLP1*	XL	• Growth failure • Hypomyelination	• Severe growth failure • Distinctive physical appearance
Cornelia de Lange syndrome	*HDAC8* *NIPBL* *RAD21* *SMC1A* *SMC3*	AD XL	Profound growth failure	Distinctive physical appearance
Dubowitz syndrome (OMIM 223370)	?	?		

Table 3. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of Cockayne Syndrome	
			Also in differential diagnosis disorder	Not in differential diagnosis disorder
Hallerman-Streiff syndrome (OMIM 234100)	?	?		
Rubinstein-Taybi syndrome	*CREBBP* *EP300*	AD		
Silver-Russell syndrome	See footnote 2			
Seckel syndrome (OMIM PS210600)	~9 genes [3]	AR		
Wiedemann-Rautenstrauch syndrome (OMIM 264090)	*POLR3A*	AR		
Congenital infections (e.g., rubella or toxoplasmosis)	N/A	N/A	Calcifications on brain imaging	• White matter hypomyelination • Distinctive physical appearance
Disorders of calcium & phosphate metabolism				
Xeroderma pigmentosum	9 genes [4]	AR	Prominent photosensitivity &/or thinning of skin & hair	• White matter hypomyelination • Brain calcifications • Ataxia • Spasticity • Neurodegenerative features
Bloom syndrome	*BLM*	AR		
Hutchinson-Gilford progeria syndrome	*LMNA*	AD		
Werner syndrome	*WRN*	AR		
Rothmund-Thompson syndrome	*RECQL4*	AR		
Mitochondrial disorders	See footnote 5	AD AR Mat	• Early presence of pigmentary retinopathy • Brain calcifications • Neurodegeneration	• Skin photosensitivity • Distinctive physical appearance

? = unknown; AD = autosomal dominant; AR = autosomal recessive; COFS = cerebrooculofacioskeletal syndrome; CS = Cockayne syndrome; Mat = maternal; MOI = mode of inheritance; XL = X-linked

1. Most leukodystrophies are not associated with growth failure, with the possible exception of the connatal form of Pelizaeus-Merzbacher disease.

2. Silver-Russell syndrome has multiple etiologies including: epigenetic changes that modify expression of genes in the imprinted region of chromosome 11p15.5, maternal UPD7, and (infrequently) autosomal dominant or autosomal recessive inheritance.

3. ATR, CENPJ, CEP152, CEP63, DNA2, NIN, NSMCE2, RBBP8, TRAIP

4. DDB2, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, POLH, XPA, XPC

5. Mitochondrial disorders can be caused by mutation of genes encoded by either nuclear DNA or mitochondrial DNA (see Mitochondrial Disorders Overview).

Warburg micro syndrome (OMIM PS600118), associated with biallelic pathogenic variants in *RAB18*,*RAB3GAP1*, *RAB3GAP2*, or *TBC1D20* and presenting with microcephaly, microcornea, and cataracts, may resemble CS type II / COFS syndrome at birth. However; Warburg micro syndrome is not associated with rapidly progressive neurodegeneration and has normal DNA nucleotide excision repair [Graham et al 2004].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Cockayne syndrome (CS), 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 Cockayne Syndrome

System/ Concern	Evaluation	Comment
Growth	• Measure & plot on standard growth charts. • Assessment of feeding	
Development	Developmental assessment	• To incl motor, adaptive, cognitive & speech/language evaluation • Evaluation for early intervention / special education
Neurologic	• Brain MRI • Assessment of muscle tone & for presence of contractures	
Eyes	Ophthalmologic evaluation	Possibly incl electroretinogram.
Hearing	Audiologic evaluation	Incl audiogram.
Skin	Dermatologic evaluation	
Teeth	Dental evaluation	
Skeletal	Radiographs to document skeletal dysplasia if suggestive clinical signs	
Kidneys	Laboratory evaluation of renal function	
Liver	Laboratory evaluation of liver function	
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Cockayne Syndrome

Manifestation/Concern	Treatment	Considerations/ Other
Poor growth	Feeding gastrostomy tube placement as needed	Avoid rapid ↑ in volume of feeds
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues in text following the table.	
Tremor - spasticity	• Medication for tremor (carbidopa-levodopa [Neilan et al 2008]) & spasticity (baclofen) if needed • Physical therapy to prevent joint contractures • Home safety assessments to prevent falls	
Abnormal vision and/or cataracts	• Standard treatment(s) as per ophthalmologist • Use of sunglasses for lens & retina protection	
Hearing loss	• Hearing aids may be helpful as per otolaryngologist. • Cochlear implants may be used [Van Wyhe et al 2018].	
Dental caries	Aggressive dental care to minimize caries	
Cutaneous photosensitivity	Use of sunscreens; limitation of sun exposure	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/ Other
Hypertension	Amlodipine, ACE inhibitor	
Gastroesophageal reflux	Proton pump inhibitor	

Developmental Disability / 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 if any changes are needed.
  - As required by special education law, children should be in the least restricted environment feasible at school and included in general education as much as possible and when 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 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 reassessed 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 individual 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 and in many cases, can improve it.

Social/Behavioral 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 is 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.

Surveillance

Yearly reassessment for known potential complications (e.g., hypertension, renal or hepatic dysfunction, declining vision and hearing) is appropriate [Laugel 2013, Wilson et al 2015]. See Table 6 for specific recommendations.

Table 6. Recommended Surveillance for Individuals with Cockayne Syndrome

System/Concern	Evaluation	Frequency
Diet	Dietary assessment	Biannual
Nervous system	Clinical review	Biannual
Eye	Ophthalmologic assessment (evaluation for cataracts & retinopathy)	Annual (biannual until age 4 yrs)
Hearing	Hearing assessment	Annual

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Diabetes	Blood glucose	Annual
Liver	Liver enzymes	Annual
Kidney	Kidney function; uric acid & proteinuria	Annual
Cardiovascular	Blood pressure	Annual

Agents/Circumstances to Avoid

Excessive sun exposure should be avoided.

Use of metronidazole should be avoided in any circumstance (risk of severe hepatitis) [Wilson et al 2015].

Extra vigilance is needed for opioid and sedative use due to exaggerated response to these types of medications [Wilson et al 2016].

Growth hormone (GH) levels in individuals with Cockayne syndrome (CS) may be elevated or decreased [Park et al 1994, Hamamy et al 2005]. While individuals with CS do not appear to be at increased risk for malignancy (an effect which may be due to simultaneous transcription and cell proliferation deficiency), it is theoretically possible that GH treatment could reverse this compensatory effect and promote tumor growth. Therefore, in the absence of safety and efficacy data, GH treatment cannot be recommended in individuals with CS.

Evaluation of Relatives at Risk

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

Pregnancy Management

No individuals with classic or severe CS (types I or II) have been known to reproduce. A successful (but very difficult) pregnancy has been reported in a young woman with mild CS (type III) [Lahiri & Davies 2003].

In pregnant women with CS, the limited size of the pelvis and abdomen is the major obstacle to the growth of the fetus and the major threat to pregnancy outcome. Prevention of premature labor and cesarean section under spinal anesthesia are usually needed [Lahiri & Davies 2003, Rawlinson & Webster 2003].

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, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Cockayne syndrome (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., carriers of one *ERCC6* or *ERCC8* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Note: Affected sibs will most likely be recognizable as affected within the first few years of life.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband

- Individuals with CS types I or II are not known to reproduce.
- The offspring of an individual with CS type III are obligate heterozygotes (carriers) for a pathogenic variant in *ERCC6* or *ERCC8*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ERCC6* or *ERCC8* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *ERCC6* or *ERCC8* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the CS-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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.

- **Amy and Friends**
  OCC The Bowling Green
  Village Road
  Oxton Wirral CH43 5SR
  United Kingdom
  Email: info@amyandfriends.org
  www.amyandfriends.org
- **Amy and Friends**
  Netherlands
  www.amyandfriends.nl
- **Cockayne Syndrome Network**
  PO Box 282
  Waterford VA 20197
  Phone: 703-727-0404; 865-466-4634
  Email: cockaynesyndrome@gmail.com
  cockaynesyndrome.org
- **L'Association Les P'tits Bouts**
  Bergerac 24100
  France
  Phone: 06 81 82 28 03
  www.cockayne.fr/lassociation
- **National Library of Medicine Genetics Home Reference**
  Cockayne syndrome
- **NCBI Genes and Disease**
  Cockayne syndrome
- **Xeroderma Pigmentosum Society, Inc (XP Society)**
  XP Society has material on their site related to UV protection/avoidance.
  437 Syndertown Road
  Craryville NY 12521
  Phone: 877-XPS-CURE (877-977-2873); 518-851-2612
  Email: xps@xps.org
  www.xps.org

- **GenIDA (Genetically determined Intellectual Disabilities and Autism Spectrum Disorders) Registry**
  A website for patients, families, and professionals; GenIDA hosts a specific registry for Cockayne syndrome.
  Email: genida@igbmc.fr
  www.genida.unistra.fr
- **Myelin Disorders Bioregistry Project**
  Email: myelindisorders@cnmc.org
  Myelin Disorders Bioregistry Project

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. Cockayne Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ERCC6	10q11.23	DNA excision repair protein ERCC-6	ERCC6 database	ERCC6	ERCC6
ERCC8	5q12.1	DNA excision repair protein ERCC-8	ERCC8 database	ERCC8	ERCC8

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 Cockayne Syndrome (View All in OMIM)

133540	COCKAYNE SYNDROME B; CSB
216400	COCKAYNE SYNDROME A; CSA
609412	EXCISION REPAIR CROSS-COMPLEMENTING, GROUP 8; ERCC8
609413	EXCISION REPAIR CROSS-COMPLEMENTING, GROUP 6; ERCC6

Molecular Pathogenesis

The proteins encoded by *ERCC6* and *ERCC8* both play important roles in transcription-coupled nucleotide excision repair (TC-NER), a DNA repair process that preferentially removes UV-induced pyrimidine dimers and other transcription-blocking lesions from the transcribed strands of active genes.

ERCC6 encodes DNA excision repair protein ERCC-6, which has at least seven domains that are conserved in DNA and RNA helicases. This protein appears to enhance the elongation of transcription products by RNA polymerase II, and possibly also RNA polymerases I and III.

ERCC8 encodes DNA excision repair protein ERCC-8, which is a WD-repeat (tryptophan aspartate-repeats) protein component of a large cullin4-mediated E3-ubiquitin ligase complex.

A deficiency of TC-NER is sufficient to explain the cutaneous photosensitivity of individuals with CS. It is unlikely, however, to explain the growth failure and neurodegeneration that typify CS. In contrast to CS, most individuals with xeroderma pigmentosum (XP) have normal growth and neurologic function, despite having combined deficiencies of both TC-NER and "global genome nucleotide excision repair" (GG-NER). To explain this apparent paradox, it has been suggested that CS proteins have other functions including roles in transcription reinitiation after genotoxic stress [Epanchintsev et al 2017], repair of oxidative DNA damage

[Nardo et al 2009, Ranes et al 2016], and mitochondrial metabolism [Kamenisch & Berneburg 2013, Chatre et al 2015, Scheibye-Knudsen et al 2016].

Mechanism of disease causation. CS occurs through a loss-of-function mechanism.

Table 7. Laboratory Technical Considerations for Genes Causing Cockayne Syndrome

Gene [1]	Technical Consideration
ERCC6	Most variants are predicted loss-of-function variants. Twenty-two missense variants have been reported to date [Calmels et al 2018].
ERCC8	Most variants are predicted loss-of-function variants. Thirteen missense variants have been reported to date [Calmels et al 2018].

1. Genes in alphabetic order

Table 8. Notable Pathogenic Variants in Genes Causing Cockayne Syndrome

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
ERCC6	NM_000124.3 NP_000115.1	c.3862C>T	p.Arg1288Ter	Associated w/COFS; founder variant in Finnish population [Jaakkola et al 2010, Laugel et al 2010]
ERCC8	NM_000082.3 NP_000073.1	c.966C>A	p.Tyr322Ter	Founder variant in Christian Arabs [Khayat et al 2010, Chebly et al 2018]

Variants listed in the table have been provided by the author. *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. Genes in alphabetic order

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Chapter Notes

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