GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

Cockayne Syndrome

[*Includes: Cockayne Syndrome Type A (CSA), Cockayne Syndrome Type B (CSB), Cockayne Syndrome Type I, Cockayne Syndrome Type II, Cockayne Syndrome Type III, Xeroderma Pigmentosum-Cockayne Syndrome (XP-CS)*]

Edward G Neilan, MD, PhD
Children's Hospital Boston
Harvard Medical School
Edward.Neilan@childrens.harvard.edu

Initial Posting: December 28, 2000.
Last Update: March 7, 2006.

Summary

Disease characteristics. Cockayne syndrome (referred to as CS throughout this *GeneReview*) spans a spectrum that includes: CS type I, the "classic" form; CS type II, a more severe form with symptoms present at birth [also known as cerebro-oculo-facial syndrome (COFS) or Pena-Shokeir syndrome type II]; CS type III, a milder form; and xeroderma pigmentosum-Cockayne syndrome (XP-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, or "connatal" CS, 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 seven years. CS type III is characterized by essentially normal growth and cognitive development or by late onset. Xeroderma pigmentosum-Cockayne syndrome (XP-CS) includes facial freckling and early skin cancers typical of XP and some features typical of CS, such as mental retardation, spasticity, short stature, and hypogonadism; XP-CS does not include skeletal involvement, the facial phenotype of CS, or CNS demyelination and calcifications.

Diagnosis/testing. Classic Cockayne syndrome (CS) is diagnosed by clinical findings including postnatal growth failure and progressive neurologic dysfunction along with other minor criteria; atypical cases may require molecular genetic testing. The two genes responsible for Cockayne syndrome are *ERCC6* (75% of individuals) and *ERCC8* (25% of individuals). Sequence analysis for both genes is clinically available.

Management. Educational programs and assistive devices for those with Cockayne syndrome are individualized. Physical therapy prevents contractures and maintains ambulation, while gastrostomy tube placement prevents malnutrition. Spasticity may be alleviated by medication. Hearing loss, cataracts and other ophthalmologic complications, and dental caries are treated as in the general population. Use of sunscreens and sunglasses and avoidance of excessive sun exposure are helpfiul. Surveillance includes yearly assessment for complications such as hypertension, renal or hepatic dysfunction, and declining vision and hearing.

Genetic counseling. Cockayne syndrome is inherited in an autosomal recessive manner. The parents of an affected child are both obligate carriers of an abnormal gene. Heterozygotes are asymptomatic. 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.

Reproduction has not been reported in any individual with CS. Carrier detection in at-risk family members is available on a clinical basis once the mutations have been identified in the proband. Prenatal testing may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

Cockayne syndrome (CS) is characterized by growth failure and multisystemic degeneration, with a variable rate of progression. The spectrum of CS phenotypes can be divided into three general clinical presentations:

- **Cockayne syndrome type I.** "Classic" CS in which the major features of the disease become apparent by one or two years of age
- **Cockayne syndrome type II.** A more severe connatal form with abnormalities recognized at birth or in the early neonatal period
- **Cockayne syndrome type III.** Milder/later-onset forms that are still poorly defined

Formal clinical diagnostic criteria have been proposed only for CS type I [Nance & Berry 1992]. Because of the progressive nature of CS, the clinical diagnosis of CS becomes more certain as additional signs and symptoms gradually manifest over time.

At all stages of disease progression, laboratory testing can be useful for confirming the suspected clinical diagnosis.

Classic Cockayne syndrome (CS type I) 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

Major criteria

- Postnatal growth failure (height and weight <5th centile by age 2 years)
- Progressive neurologic dysfunction manifested as early developmental delay in most individuals, followed by progressive behavioral and intellectual deterioration in all individuals; brain MRI reveals leukodystrophy [Boltshauser et al 1989, Sugita et al 1992]. Intracranial calcifications are seen in some individuals.

Minor criteria

- Cutaneous photosensitivity with or without thin or dry skin or hair (~75%)
- Demyelinating peripheral neuropathy diagnosed by electromyography, nerve conduction testing, and/or nerve biopsy
- Pigmentary retinopathy (~55%) and/or cataracts (~36%)
- Sensorineural hearing loss (~60%)
- Dental caries (~86%)
- A characteristic physical appearance of "cachectic dwarfism" with thinning of the skin and hair, sunken eyes, and a stooped standing posture

- Characteristic radiographic findings of thickening of the calvarium, sclerotic epiphyses, vertebral and pelvic abnormalities

Family history

- The presence of a similarly affected sib can be useful for diagnosis.

Connatal Cockayne syndrome (CS type II) 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 with other structural defects of the eye (microphthalmos, microcornea, iris hypoplasia) are present

Testing

Assay of cellular phenotype

- **DNA repair assay.** Assays of DNA repair are performed on skin fibroblasts. The most consistent findings in CS fibroblasts are: marked sensitivity to UV radiation; deficient recovery of RNA synthesis following UV damage; and impaired repair of actively transcribed genes, or "transcription-coupled repair" [Venema et al 1990, Troelstra et al 1992, van Gool et al 1997]. DNA repair assays are available on a research basis only.
- **Complementation groups.** Cells from individuals with CS can be divided into two complementation groups based on the protein that corrects the DNA repair defect: the CS WD-repeat protein CSA in Cockayne syndrome-A (25% of individuals) and the excision repair protein ERCC-6 in Cockayne syndrome-B (75% of individuals) [Stefanini et al 1996]. Complementation studies are available on a research basis only.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Genes. Two genes are known to be associated with Cockayne syndrome:

- ***ERCC8 (CKN1).*** Mutations in *ERCC8* cause Cockayne syndrome type A (CSA), which accounts for 25% of cases [Henning et al 1995].
- ***ERCC6.*** Mutations in the excision repair cross-complementing group 6 gene *(ERCC6*) cause Cockayne syndrome type B (CSB), which accounts for 75% of cases [Troelstra et al 1992, Troelstra et al 1993].

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Carrier testing

Molecular genetic testing: Clinical method

- **Sequence analysis**

- ***ERCC8 (CKN1).*** Approximately 70% of the pathogenic mutations reported in *ERCC8* are missense, nonsense, or splice-site mutations that are detectable by sequence analysis. The other 30% are large, partial deletions of *ERCC8* that escape detection by sequence analysis, if present in a heterozygous state or compound heterozygous state [Henning et al 1995, Ren et al 2003, Cao et al 2004].
- ***ERCC6.*** Nearly all of the known pathogenic mutations in *ERCC6* are point mutations that are detectable by sequence analysis. A large majority of these are nonsense or frameshift mutations that are predicted to result in the formation of a truncated protein [Troelstra et al 1992, Mallery et al 1998, Colella et al 1999, Meira et al 2000, Horibata et al 2004].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Cockayne Syndrome

Subtype of Cockayne Syndrome	% of Affected Individuals	Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Cockayne syndrome type A (CSA)	25%	Sequence analysis	Point mutations or small insertions/ deletions in *ERCC8*	~70%	Clinical Testing
Cockayne syndrome type B (CSB)	75%		Point mutations or small insertions/ deletions in *ERCC6*	>95%	Clinical Testing

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

Testing Strategy for a Proband

Because approximately 75% of Cockayne syndrome is caused by mutations in the *ERCC6* gene and most of the remaining 25% by mutations in the *ERCC8* gene, *ERCC6* is sequenced first. If no mutation is identified, *ERCC8* is then sequenced.

Genetically Related (Allelic) Disorders

ERCC6. Mutations in *ERCC6* have also been identified in individuals with:

- Cerebro-oculo-facial-skeletal syndrome (COFS), now recognized to be part of the spectrum of Cockayne syndrome [Meira et al 2000]
- DeSanctis-Cacchione variant of xeroderma pigmentosum (XP) [Colella et al 2000].
- UV-sensitive syndrome (UVSS) [Horibata et al 2004]

ERCC8. No other phenotypes are associated with mutations in *ERCC8*.

Clinical Description

Natural History

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 spectrum that includes: CS type I, the "classic" form [Lowry 1982]; CS type II, a more severe form with symptoms present at birth (previously called cerebro-oculo-facio-skeletal syndrome (COFS) and Pena-Shokeir type II syndrome); CS type III, a milder form; and xeroderma pigmentosum-Cockayne syndrome (XP-CS) [Nance & Berry 1992].

Biochemical assays of DNA repair function and molecular genetic testing of DNA repair genes have not yet completely clarified the classification of these disorders, as mutations in the same gene can cause mild to severe phenotypes, while different biochemical characteristics can be present in individuals with a similar clinical phenotype. Some individuals with the COFS phenotype have biochemical characteristics of the xeroderma pigmentosum-D (XP-D) and xeroderma pigmentosum-G (XP-G) complementation groups, suggesting that Cockayne syndrome and COFS do not overlap completely on a biochemical basis [Graham et al 1988, Moriwaki et al 1996]. These diagnostic dilemmas are discussed in detail in Rapin et al 2000.

CS type I. 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. Progressive impairment of vision, hearing, and central and peripheral nervous system function leads to severe disability. Severe dental caries occur in up to 86% of individuals. Photosensitivity can be severe, 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, abnormal gait or inability to walk, ataxia, incontinence, tremor, abnormal or absent speech, seizures, weak cry/poor feeding (as an infant), muscle atrophy, and behavioral abnormality
- **Dermatologic.** Anhidrosis and malar rash
- **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, and microphthalmia
- **Dental.** Absent or hypoplastic teeth, delayed eruption of deciduous teeth, and malocclusion
- **Renal.** Abnormal renal function and pathologic abnormalities have been noted in case reports, but are usually not clinically significant.
- **Endocrine.** Undescended testes, delayed/absent sexual maturation. No individuals with classic or severe/connatal 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].
- **Gastrointestinal.** Elevated liver function tests, enlargement of liver or spleen

Death typically occurs in the first or second decade. The mean age of death is 12 years, but survival into the third decade has been reported.

CS type II. Children with "connatal" 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 have arthrogryposis or early postnatal contractures of the spine (kyphosis, scoliosis) and joints. Affected children typically die by age seven years. CS type II overlaps clinically with the cerebro-oculo-facial syndrome (COFS), which is also referred to as Pena-Shokeir syndrome type II. Following the identification of a mutation in *ERCC6* in a family with COFS [Meira et al 2000], it was recognized that Cockayne syndrome type II is the correct diagnosis for individuals previously said to have COFS or Pena-Shokeir syndrome type II who have *ERCC8* or *ERCC6* mutations or characteristic DNA repair abnormalities.

CS type III. Recently, 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 exceed the expectations for CS type I [E Neilan, unpublished].

Xeroderma pigmentosum-Cockayne syndrome (XP-CS). Since the discovery of the genes underlying CS, it has become evident that the distinctions between genotype, cellular phenotype, and clinical phenotype are not absolute. Xeroderma pigmentosum, a related DNA repair disorder, includes facial freckling and early skin cancers — features not found in CS. The DeSanctis-Cacchione variant of XP includes some features of CS such as mental retardation, spasticity, short stature, and hypogonadism, but does not include skeletal dysplasia, the facial phenotype of CS, or CNS demyelination and calcifications. Individuals with an XP clinical phenotype have been seen in association with a CS cellular phenotype and with a mutation in the *ERCC6* gene [Greenhaw et al 1992, Colella et al 2000]. Conversely, individuals with clinical features of CS but with XP-like skin cancers have been assigned to the XPB, XPD, and XPG complementation groups based on their biochemical characteristics (the ability to restore normal function to various DNA repair-deficient cell lines) [Okinaka et al 1997, Riou et al 1999, Van Hoffen et al 1999]. Individuals with other features of CS, but lacking sun sensitivity, have been reported. Mallery et al (1998) has reported a poor correlation between genotype and phenotype for this group of diseases.

Neuropathology. 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, is observed [Itoh et al 1999].

Genotype-Phenotype Correlations

It is not yet clear whether genotype-phenotype correlations exist in Cockayne syndrome.

Early reports found no obvious genotype-phenotype correlations for mutations in either *ERCC8* or *ERCC6*, suggesting that the clinical variability within the CS spectrum may not be accounted for by gene mutation alone.

More recently, however, it has been reported that a null mutation of *ERCC6* does not produce CS, but instead produces the mild UV-sensitive syndrome [Horibata et al 2004]. This would imply the existence of genotype-phenotype correlations in CS, at least in cases involving *ERCC6*.

Nomenclature

The term cerebro-oculo-facio-skeletal syndrome (COFS) and its synonym, Pena-Shokeir syndrome type II, refer to a group of genetically heterogeneous disorders characterized by congenital neurogenic arthrogryposis (multiple joint contractures), microcephaly, microphthalmia and cataracts. Mutations in at least three genes account for the phenotype; therefore, the term COFS should be reserved for those individuals in whom a more precise genetic diagnosis cannot be made.

- The original cases of COFS, described by Pena and Shokeir in 1974 among native Canadian families from Manitoba, have since been shown to be homozygous for a mutation in *ERCC6*. Cells from these individuals show the same deficiency of transcription-coupled DNA nucleotide excision repair (TC-NER) as cells from those with CS. It is advisable to say that these individuals have CS type II, rather than COFS.
- Other persons with COFS have a global deficiency of nucleotide excision repair resulting from mutations in the xeroderma pigmentosum genes *XPG* or *XPD*.

- Others diagnosed with COFS have no demonstrable DNA repair defect and presumably are affected because of mutations in a distinct, as-yet-unknown gene.

Prevalence

The prevalence of CS is unknown; essentially all cases have been reported as single cases or family reports. The figure generally used for the frequency of rare disorders is 1/100,000; CS is likely rarer. At least 140 individuals with CS had been reported in the literature up to 1992 [Nance & Berry 1992]. CS has been reported to be more common in population isolates or inbred populations. The genetically related disorder COFS was originally reported in an isolated native population in Manitoba, Canada.

Differential Diagnosis

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

The differential diagnosis of CS depends on the presenting features of the particular individual. Abnormalities that suggest alternative diagnoses are 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 [Nance & Berry 1992].

- Growth failure is seen in chromosomal disorders and endocrine, metabolic, or gastrointestinal disorders, including malnutrition.
- Most leukodystrophies are not associated with growth failure, with the possible exception of the connatal form of Pelizaeus-Merzbacher disease.
- The presence of calcifications on brain imaging could suggest congenital infections such as rubella or toxoplasmosis, or disorders of calcium and phosphate metabolism.
- If photosensitivity or thinning of the skin and hair are prominent, the differential diagnosis includes xeroderma pigmentosum, Bloom syndrome, and the "premature aging" syndromes such as Hutchinson-Gilford progeria syndrome, Werner syndrome, and Rothmund-Thompson syndrome.
- The early presence of pigmentary retinopathy could suggest a mitochondrial disorder (see Mitochondrial Disorders Overview) or a peroxisomal biogenesis disorder (see Peroxisomal Biogenesis Disorder, Zellweger syndrome spectrum).
- Syndromes with profound growth failure (e.g., Cornelia de Lange syndrome, Dubowitz syndrome, Hallerman-Streiff syndrome, Rubinstein-Taybi syndrome, Russell-Silver syndrome, Seckel syndrome, and Wiedemann-Rautenstrauch syndrome) can usually be excluded on the basis of physical appearance.
- MICRO syndrome can resemble CS type II/COFS at birth, presenting with microcephaly, microcornea, and cataracts. It differs by the absence of rapidly progressive neurodegeneration and by the presence of normal DNA nucleotide excision repair [Graham et al 2004].

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Measurement of growth
- Developmental assessment
- Dental evaluation

- Dermatologic evaluations
- Ophthalmologic evaluations (possibly including electroretinogram)
- Audiologic evaluation (including audiogram)
- Brain MRI
- Laboratory studies to assess renal and hepatic function
- Testing for diabetes mellitus and disorders of calcium metabolism
- Skeletal x-rays to document the presence of skeletal dysplasia
- Nerve conduction studies to document the presence of a demyelinating neuropathy

Treatment of Manifestations

- An individualized educational program for developmental delay
- Physical therapy and assistive devices to maintain ambulation in the presence of gait abnormalities
- Feeding gastrostomy tube placement for failure to thrive
- Medication for spasticity
- Management of hearing loss
- Management of cataracts and other ophthalmologic complications
- Use of sunscreens for cutaneous photosensitivity

Prevention of Primary Manifestations

Use of sunglasses to possibly reduce the risk of cataract formation

Prevention of Secondary Complications

- Physical therapy to prevent joint contractures
- Aggressive dental care to minimize dental caries
- Home safety assessments to prevent falls

Surveillance

Yearly reassessment for known potential complications such as hypertension, renal or hepatic dysfunction, and declining vision and hearing

Testing of Relatives at Risk

Regular growth and developmental assessments and possibly also diagnostic laboratory testing for younger siblings who are still infants or toddlers

Agents/Circumstances to Avoid

Excessive sun exposure

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Growth hormone (GH) levels in individuals with Cockayne syndrome may be elevated or decreased [Park et al 1994, Hamamy et al 2005]. GH-deficient individuals with CS could logically benefit from its use. However, this has not been established; a trial of GH in one individual did not improve growth [Windmiller et al 1963].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Cockayne syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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. It can safely be assumed that all homozygous individuals will be recognizable as affected within the first few years of life.
- Once an at-risk sib is known to be unaffected, the chance of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. Reproduction has not been reported in any individual with CS types I or II, and in only one woman with CS type III. Each offspring of an affected person is an obligate carrier.

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

Carrier Detection

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

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and clarification of carrier status is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of Cockayne syndrome are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which disease-causing mutations have been identified in an affected family member in a research or clinical lab. For labs offering custom prenatal testing, see Testing.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

The reported gene mutations in Cockayne syndrome have been summarized [Cleaver et al 1999].

Table A. Molecular Genetics of Cockayne Syndrome

Complementation Group	Gene Symbol	Chromosomal Locus	Protein Name
Cockayne Syndrome-A (CSA)	*ERCC8*	Chr.5	Cockayne syndrome WD-repeat protein CSA
Cockayne Syndrome-B (CSB)	*ERCC6*	10q11	DNA excision repair protein ERCC-6

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Cockayne Syndrome

133540	COCKAYNE SYNDROME, TYPE B; CSB
216400	COCKAYNE SYNDROME, TYPE A; CSA

Table C. Genomic Databases for Cockayne Syndrome

Gene Symbol	Entrez Gene	HGMD
ERCC8	1161 (MIM No. 216400)	ERCC8
ERCC6	2074 (MIM No. 133540)	ERCC6

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

Molecular Genetic 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. 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, a critical role of the *ERCC6* and *ERCC8* gene products outside of TC-NER has been suggested, such as an auxiliary function in transcription and/or in non-NER forms of DNA repair [de Waard et al 2004, van den Boom et al 2004].

***ERCC8*—Normal allelic variants:** The dbSNP database lists several common single nucleotide polymorphisms (SNPs) that are located within the coding sequence of *ERCC8*. Cao et al (2004) have reported another.

Pathologic allelic variants: Several mutations in the *ERCC8* gene have been identified, including nonsense mutations, missense mutations, and large, partial deletions of the gene [Hennng et al 1995, Ren et al 2003, Cao et al 2004]. No single mutation seems to predominate. Intriguingly, Komatsu et al (2004) recently reported finding multiple abnormal *ERCC8* mRNA splice variants in an individual with CS, although they were unable to identify the DNA mutations responsible for these mRNA splicing abnormalities.

Normal gene product: The *ERCC8* gene encodes a 396-amino acid protein of 44 kd. It is a WD-repeat protein, which interacts with the excision repair protein ERCC-6 and the p44 protein. The p44 protein is a subunit of TFIIH, an RNA polymerase II transcription factor. Both *ERCC8* and *ERCC6* appear to be involved in transcription-coupled DNA repair, and possibly in other processes [de Waard et al 2004].

Abnormal gene product: The pathogenic abnormalities thus far reported in the *ERCC8* gene vary from large, partial deletions of the gene that remove entire exons to missense mutations that alter a single amino acid [Henning et al 1995, Ren et al 2003, Cao et al 2004].

***ERCC6*—Normal allelic variants:** The dbSNP database lists more than a dozen common single nucleotide polymorphisms (SNPs) that are located within the coding sequence of *ERCC6*.

Pathologic allelic variants: More than 20 different mutations have been reported in the *ERCC6* gene. Most of these are nonsense or frameshift mutations [Troelstra et al 1992, Mallery et al 1998, Colella et al 1999, Meira et al 2000, Horibata et al 2004].

Normal gene product: The ERCC6 gene encodes a 1493-amino acid protein, containing 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. Both *ERCC8* and *ERCC6* appear to be involved in transcription-coupled DNA repair [Licht et al 2003, van den Boom et al 2004].

Abnormal gene product: A large majority of the pathogenic mutations reported in *ERCC6* are nonsense or frameshift mutations that would be predicted to encode a truncated protein.

This somewhat unusual mutation spectrum suggests that the pathogenic mechanism may not be as simple as a loss of *ERCC6*'s normal functions. Indeed, Horibata et al (2004) report that in at least one case, a homozygous null mutation of *ERCC6* failed to produce CS, causing instead only the much milder UV-sensitive syndrome.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Cockayne Syndrome Network
P.O. Box 282
Waterford VA 20197
Phone: 703-265-3719
Fax: 972-613-4590
Email: JackieClark@aol.com
www.cockayne-syndrome.org

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: Email: xps@xps.org
www.xps.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

American Res of Pathology. Xeroderma pigmentosum and Cockayne Syndrome: A Multimedia Overview. Copyright 1998. 1998

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Chapter Notes

Author History

Martha A Nance, MD; Park Nicollet Clinic (2000-2006)
Edward G Neilan, MD, PhD (2006-present)

Revision History

- 7 March 2006 (me) Comprehensive update posted to live Web site
- 24 September 2003 (cd) Revision: clinical test no longer available
- 21 August 2003 (cd) Revision: change in gene name
- 31 July 2003 (me) Comprehensive update posted to live Web site
- 15 October 2001 (mn) Author revision
- 28 December 2000 (me) Review posted to live Web site
- June 2000 (mn) Original submission