HHS Public Access

Author manuscript

Ageing Res Rev. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Ageing Res Rev. 2017 January ; 33: 3–17. doi:10.1016/j.arr.2016.08.002.

Cockayne syndrome: Clinical features, model systems and pathways

Ajoy C. Karikkineth[a], **Morten Scheibye-Knudsen**[b,c], **Elayne Fivenson**[b], **Deborah L. Croteau**[b], and **Vilhelm A. Bohr**[b,d]

[a]Clinical Research Branch, National Institute on Aging, Baltimore, MD, USA

[b]Laboratory of Molecular Gerontology, National Institute on Aging, Baltimore, MD, USA

[c]Department of Cellular and Molecular Medicine, University of Copenhagen, Denmark

Abstract

Cockayne syndrome (CS) is a disorder characterized by a variety of clinical features including cachectic dwarfism, severe neurological manifestations including microcephaly and cognitive deficits, pigmentary retinopathy, cataracts, sensorineural deafness, and ambulatory and feeding difficulties, leading to death by 12 years of age on average. It is an autosomal recessive disorder, with a prevalence of approximately 2.5 per million. There are several phenotypes (1, 2 and 3) and complementation groups (CSA and CSB), and overlaps with xeroderma pigmentosum (XP). It has been considered a progeria, and many of the clinical features resemble accelerated aging. As such, the study of CS affords an opportunity to better understand the underlying mechanisms of aging. The molecular basis of CS has traditionally been considered to be due to defects in transcription and transcription-coupled nucleotide excision repair (TC-NER). However, recent work suggests that defects in base excision DNA repair and mitochondrial functions may also play key roles. This opens up the possibility of molecular interventions in CS, and by extrapolation, possibly in aging.

Keywords

Cockayne syndrome; progeria; neurodegeneration; mitochondria; transcription; parylation

1.0 Introduction

Cockayne syndrome, also called Neill-Dingwall syndrome was first described in 1936 by Edward Cockayne in a paper titled “Dwarfism with retinal atrophy and deafness (Cockayne, 1936).” Ten years later he reported follow up data for the same patients, with new clinical features of progressive hearing loss, visual dysfunction and joint contractures (Cockayne,

[d]Corresponding author: Vilhelm A. Bohr, vbohr@nih.gov.

1946). Mary M. Dingwall and Catherine A. Neill also described the disease in two brothers, and noted the presence of calcifications in the brain (Neill and Dingwall, 1950).

A landmark study by Nance and Berry reviewed 140 patients with CS (Nance and Berry, 1992), and provided detailed information on many of the clinical features. They proposed a classification system of CS into 3 types, and also major and minor criteria for the diagnosis of CS. Subsequent reviews by Rapin, Kubota, Wilson and others (Kubota et al., 2015; Laugel, 2013; Natale, 2011; Rapin et al., 2006; Wilson et al., 2015) have helped improve the understanding of this disease.

CS has an incidence of 1 in 250,000 live births, and a prevalence of 2.5 per million, which is remarkably consistent across various regions globally (Kubota et al., 2015; Nance and Berry, 1992; Wilson et al., 2010). Table 1 summarizes the clinical features commonly seen in CS, while Table 2 highlights some of the important similarities and differences from reviews of CS. Table 3 shows the distribution by location of the different histopathological changes commonly seen in the nervous system.

CS has a spectrum of clinical severity (see section 3.1 on Genetics below). The typical phenotype includes cachectic dwarfism, shriveled and wrinkled skin, loss of subcutaneous fat, beaked nose (Figure 1), and stooped posture. Some patients with CS have an extreme sensitivity to sunlight; even a small amount of sun exposure can cause sunburn. The diagnosis of CS has been based on the lack of recovery of RNA transcription after UV light-induced DNA damage. As such, CS has been considered a disorder of transcription-coupled nucleotide excision repair. However, additional mechanisms such as transcription defects, persistent PARylation, and mitochondrial dysfunction may better explain some of the clinical manifestations seen in CS (see sections 4.2, 4.3 and 4.4).

CS recapitulates normal human aging in many of its clinical features. Cognitive dysfunction, sensorineural deafness and high tone hearing loss are observed in CS and in normal aging. Additionally, the advanced atherosclerosis and vasculopathy of CS (Crome and Kanjilal, 1971; Hayashi et al., 2012; Itoh et al., 1999) (section 2.4 & Table 1) resemble changes that occur in aged normal individuals. Further similarities conserved between CS and the aging phenotype include the premature onset of hypertension, which often leads to strokes, and renal and cardiac dysfunction (Fujimoto et al., 1969; Higginbottom et al., 1979; Yuen et al., 2001) (section 2.4 and Table 1). Cataracts are seen in CS and are very common in normal human aging (“Cataracts | National Eye Institute,” n.d.; Lowry et al., 1971; Nance and Berry, 1992) (Section 2.2 & Table 1). A better understanding of CS, its molecular mechanisms and possible interventions can thus likely provide insight in understanding normal human aging.

2.0 Clinical features of CS

2.1 Hearing

Sensorineural high tone hearing loss has been considered to be a cardinal feature of CS (Cockayne, 1936; Nance and Berry, 1992), and is due to cell loss at multiple sites along the auditory pathways (Table 1 & Figure 3G). Both the type of the hearing loss and the pattern

of cell loss mimic that seen in normal individuals as they age. Some evidence of anatomical abnormalities of the inner and middle ear have been reported (Rapin et al., 2006)(Table 1), and these may lead to conductive deafness (Wilson et al., 2015). While some reports indicate that the onset could be sudden (Natale, 2011), it is mostly considered a slowly progressive disorder. If not diagnosed early, hearing loss could lead to a relatively more withdrawn personality (Natale, 2011).

The prevalence of hearing loss is impacted by the severity of disorder. Some patients manifested hearing loss after 2–3 years of age (Kubota et al., 2015). More severely affected individuals may have neonatal hearing loss (Wilson et al., 2015). Other CS patients have mild and late hearing impairment (Laugel, 2013). Earlier reports indicated a delayed onset of hearing loss in the teenage years (Nance and Berry, 1992)(Table 2), which could reflect individuals with milder disease, or difficulties in detecting hearing loss in certain patients.

Audiometry testing is frequently unavailable for various reasons, including difficulty of testing in children, and neurological and cognitive impairment. In a study examining auditory brainstem responses and behavioral audiometry in four CS patients (Iwasaki and Kaga, 1994), behavioral tests were evaluated in all four cases, and brainstem auditory evoked potentials showed varying changes, from abnormally delayed auditory brainstem response components to complete absent auditory brainstem responses. This could be representative of different severities of the disease or a wide variation in clinical presentation. These tests could represent progression of disease, with spread of involvement from the upper brainstem to the cochlear nerve (Iwasaki and Kaga, 1994), although other authors believe that the involvement of the brainstem auditory pathways and cochlear deficits are separate events (Scaioli et al., 2004). There may be a loss of neurons in the auditory pathway nuclei in the brainstem, but there is generally no involvement of the higher auditory relays (Iwasaki and Kaga, 1994).

The severity of hearing loss seems well correlated with the overall severity of the disease process (Laugel, 2013). Auditory brainstem response deterioration may reflect the progression of neurodegeneration better than visual evoked potentials, electroretinograms, or somatosensory evoked potentials (Scaioli et al., 2004).

2.2 Vision

Cataracts have been consistently reported among CS patients (Kubota et al., 2015; Lowry et al., 1971; Nance and Berry, 1992; Wilson et al., 2015) (Table 2 & Figure 3D). The occurrence of cataracts before 3 years of age may be the most important prognostic factor for survival in CS patients, with such patients having a significantly worse probability of survival, and most such patients may die before the age of 7 (Nance and Berry, 1992; Wilson et al., 2015). Early cataracts are also associated with earlier development of hearing loss and contractures (Wilson et al., 2015), and congenital cataracts are predictors of early onset, severe disease or overlap with Cerebro-oculo-facio-skeletal (COFS) syndrome (Laugel, 2013). However, cataracts that develop in later ages may be distributed across all severity groups more evenly, and may not have the same prognostic implications as early onset cataracts (Natale, 2011).

Cataract surgery performed at an early stage, as soon as possible after detection, and before the progression of retinal dystrophy, ideally within the first 3 months of life in cases of congenital cataracts, reduces the risk of visual loss and offers improved clinical outcome (McElvanney et al., 1996).

The combination of miotic pupils, poor response to mydriatics, and anatomical abnormalities such as enophthalmos, make cataract surgery difficult. (McElvanney et al., 1996). Post-operatively, many individuals rapidly develop posterior lens opacification, and often need repeat surgery. Intraocular lenses are controversial in children aged less than 2 years old, and so contact lenses are usually prescribed, but these might be difficult to fit due to the anatomical abnormalities, and spectacles might be needed (McElvanney et al., 1996).

Retinal dystrophy has long been recognized as a feature of CS, and was part of the title of the initial report on the disorder by Cockayne (Cockayne, 1936). It is considered as one of the hallmarks of the disease, and presents typically with abnormal retinal pigmentation in a salt and pepper pattern (Figure 2). It is progressive throughout life, and only becomes clinically significant in advanced stages of the disease. Optic disk pallor is frequently associated with retinal degeneration, but may precede the retinal abnormalities. Other retinal changes such as hemorrhage and atrophy are seen in less than 5 percent of patients (Nance and Berry, 1992). However, a normal retina early in life does not rule out CS, as the ophthalmologic changes are progressive (Rapin et al., 2006, p. 200). Electroretinograms may be abnormal long before any clinical impairment (Rapin et al., 2006). Retinal dystrophy may co-exist with cataracts, but more commonly the onset of cataracts precedes retinal dystrophy by many years.

The severity of the retinal degeneration, and specifically of the electroretinogram anomalies, seem to parallel the overall severity of the disease (Laugel, 2013). Pigmentary retinopathy is not seen as part of the normal clinical spectrum of human aging, but may be seen in other diseases such as peroxismal disorders, and mitochondrial disorders such as Kearns Sayre syndrome and mitochondrial encephalomyopathy with ragged-red fibers, and these disorders must be excluded in the diagnostic approach (Nance and Berry, 1992).

Other visual abnormalities reported include photophobia; corneal abnormalities such as opacification (band keratopathy), xerophthalmia (dry eyes), corneal ulcers and a small cornea; and other abnormalities such as hyperopia (far sightedness), strabismus, nystagmus, localized posterior deformation of the lens (posterior lentiglobus), and microphthalmos (Coles, 1969; Dollfus et al., 2003; McElvanney et al., 1996; Traboulsi et al., 1992a) (Table 1). The eyelid opening may have to be surgically narrowed (tarsorrhaphy) as treatment for calcific band keratopathy and corneal inflammation (McElvanney et al., 1996). The small constricted pupils may respond poorly to pupillary dilators, and thus, make funduscopic examinations difficult.

2.3 Neurological manifestations

The neurological manifestations of CS are devastating and account for a significant portion of the morbidity of the disease (Figure 3). There are no major somatic or brain deformations. The cortex is relatively preserved until the late stages, and this has been postulated to be the

reason for the preservation of social skills until late in the disease (Koob et al., 2010). Cerebellar involvement is very severe in CS patients (Rapin et al., 2006)(Table 1 & Figure 3C). The basal ganglia nuclei and thalamus are second to the cerebellum in the severity of their pathology, with considerable variation among cases as to the nuclei most affected. Neurons in the brainstem nuclei and spinal cord are variably involved (Table 1 & Figure 3H). Loss of anterior horn cells and dorsal root ganglion cells in individuals in whom the neuropathy has become mixed may be examples of retrograde as well as anterograde neuronal degeneration (Mizuguchi and Itoh, 2005; Weidenheim et al., 2009).

Abnormal myelin, the fatty covering that acts as an insulator around the nerve fiber, is one of the key characteristics of CS, although it is not settled whether this myelinopathy is developmental, degenerative, or both. The myelinopathy affects both central and peripheral myelin (Mizuguchi and Itoh, 2005), indicating the involvement of both oligodendroglia and Schwann cells in the disease process (Rapin et al., 2006; Weidenheim et al., 2009). The oligodendroglia are depleted in demyelinated areas in the patches of central demyelination, but preserved in the perivascular areas, changes that characterize the “tigroid leukodystrophy” of CS (Rapin et al., 2006) (Figure 3B). Leukodystrophy is the progressive degeneration of the white matter of the brain due to imperfect growth or development of the myelin sheath, the fatty covering that acts as an insulator around the nerve fiber (Figure 3E). This leukodystrophy may affect the cerebral cortex, corpus callosum and internal capsule to a greater extent than the cerebellum and brain stem, which may have normal myelination (Weidenheim et al., 2009). Complete absence of myelination from the first year of life was observed in patients with the most severe COFS and CS disease, while in less severe cases, it may be arrested at a stage comparable to that in a 6 month old normal child (Weidenheim et al., 2009).

There is severe cerebral white matter atrophy in CS (Figure 4). Brain atrophy was seen in all patients who had magnetic resonance (MR) imaging in one series, and the white matter loss seemed to be the earliest neuro-radiologic finding (Koob et al., 2010). Overall, the degree of cortical atrophy is not correlated with the age of the patient, although this correlation might be better when each subtype of CS is considered individually (Koob et al., 2010; Rapin et al., 2006; Weidenheim et al., 2009).

The severe cerebral white matter atrophy leads to microcephaly. Microcephaly is considered a cardinal feature of CS along with growth retardation, and progressive microcephaly has been proposed as the third major criterion of CS (Laugel, 2013). Head circumference at birth is usually normal, and congenital microcephaly may be indicative of severe forms of CS or COFS (Nance and Berry, 1992). The rate of increase of the head circumference after birth is slow, gets slower with age, and often comes to a complete stop between 1–2 years of age. Almost all patients with CS over 2 years of age have microcephaly, although a small percentage may have normal measurements. However, in the typical patient suspected of having CS in the absence of microcephaly, an alternative diagnosis should be considered (Nance and Berry, 1992). The severity of microcephaly varies widely. Autopsied brains from CS individuals generally weighed 50% or less than expected in normal at the chronological age (Rapin et al., 2006). Mean head circumference of CS type 1 patients has been reported as −7.34 ± 2.96SD (median standardized values) (Wilson et al., 2015), and may be

consistently below −3SD (Laugel, 2013). The degrees of microcephaly, growth failure, neurological and sensorial impairment are usually grossly related (Nance and Berry, 1992; Rapin et al., 2006; Weidenheim et al., 2009; Wilson et al., 2015).

Multiple studies have demonstrated the presence of peripheral neuropathy in patients with CS (Campistol Plana et al., 1991; Grunnet et al., 1983; Scaioli et al., 2004; Schenone et al., 1986; Vos et al., 1983; Weidenheim et al., 2009). This may lead to neurogenic bladder, muscle atrophy, hyperreflexia or areflexia, and locomotion disturbances. Age of symptom onset may be variable (Rapin et al., 2006), although the majority of patients have signs of diffuse peripheral neuropathy measured by nerve conduction studies from the early stages of the disease (Nance and Berry, 1992). CS is primarily a demyelinating neuropathy, although there may be a small component of an axonal neuropathy (Scaioli et al., 2004), and it involves both sensory and motor systems. Increasingly slow nerve conduction velocity testifies to the progressive nature of the neuropathy.

Bilateral calcification of the basal ganglia, dentate nucleus, and subcortical white matter are diagnostic hallmarks of CS (Table 2 & Figure 4), but genetically confirmed CS without calcification has been reported in rare cases (Boltshauser et al., 1989; Demaerel et al., 1992, 1990; Jin et al., 1979; Soffer et al., 1979). Brain calcification may not appear before the age of 1, even in severe types of CS, but almost all CS patients develop calcification after the age of 3 years (Koob et al., 2010). Microscopic examination has suggested the presence of iron, thus pointing to the possibility of a more complex mineralization than simple calcification (Wilson et al., 2015). Overall, there was no strict correlation between the extent or severity of the calcifications and the age of the patients, the severity of their neurologic symptoms, or the degree of cerebral atrophy (Koob et al., 2010). The patterns of calcification are not pathognomonic or clinically actionable (Kubota et al., 2015; Wilson et al., 2015). Nevertheless, the largest calcifications are often seen in the oldest patients (Koob et al., 2010). The most severely affected patients had almost identical distribution of calcification (Koob et al., 2010). Calcifications can be seen on CT scans as well as MRI scans of the brain. Quantitation may help with documenting the severity of the calcification (Koob et al., 2010), but this has not been validated. Susceptibility weighted MRI may be more sensitive than regular MRI to detect calcifications seen in Cockayne’s syndrome (Wagner et al., 2014).

Astrocytosis and microcytosis are prominent in CS (Figure 3E), but it is not clear whether these are reactive to neuronal loss and myelin loss or whether they represent primary involvement of astrocytes and microcytes (Koob et al., 2010). Frequent large, bizarre, or multinucleated astrocytes are common in CS (Rapin et al., 2006; Weidenheim et al., 2009), and this has been postulated to be due to defective transcription-coupled nucleotide excision repair (Brooks, 2013; Brooks et al., 2008; Hayashi et al., 2005; Jaarsma et al., 2011; Rapin et al., 2006; Weidenheim et al., 2009).

The severe involvement of the nervous system leads to cognitive dysfunction and mental retardation. Milestones are delayed. Hearing and visual loss adds to the cognitive dysfunction (Weidenheim et al., 2009). Individuals with CS develop motor dysfunction and ambulatory difficulties. Seizure disorders and tremor affect around 23% and 66% of CS

patients, respectively (Wilson et al., 2015). In the majority of affected patients seizures are ongoing, and there is no predominant seizure type. Tremor is most often an intention tremor (Wilson et al., 2015), consistent with a cerebellar etiology; in some cases onset is associated with apparent developmental regression, as children become less skilled in fine and gross motor domains. CS patients with tremor might respond to carbidopa-levodopa (Neilan EG et al., 2008), although very few patients outside of clinical trials have received such treatment (Kubota et al., 2015; Wilson et al., 2015). Ataxia can be prominent, due to a combination of impairment of the cerebellum, vision, vestibular systems, and impaired input from the extremities due to peripheral neuropathy (Mizuguchi and Itoh, 2005).

2.4 Other organ systems

The cardiovascular system shows advanced-for-age atherosclerosis (Crome and Kanjilal, 1971; Hayashi et al., 2012). Calcific vasculopathy has been documented, especially in the leptomeningeal vessels (Weidenheim et al., 2009). There may be accelerated hypertension. Some structural abnormalities have also been infrequently described (Table 1)(Ovaert et al., 2007; Yuen et al., 2001).

Feeding is often difficult in CS patients. Many have severe gastroesophageal reflux disease. Tolerance of oral nutrition is often poor, and they often have accelerated muscle wasting. As such many patients may require percutaneous gastrostomy tubes. One explanation for weight loss might be an increased metabolism, and a high fat diet has been shown in mouse models to attenuate the high metabolic rate (Scheibye-Knudsen et al., 2014b).

Renal failure may occur in CS patients (Kubota et al., 2015). Some individuals may have anatomical abnormalities such as unilateral or hypoplastic kidneys, but in the majority of patients with renal dysfunction it is thought to be secondary to hypertension and atherosclerosis/arteriolosclerosis (Bartenjev et al., 2000; Higginbottom et al., 1979; Hirooka et al., 1988; Pasquier et al., 2006). Renal failure may be a marker of poor prognosis, and may indicate impending death (Kubota et al., 2015).

2.5 Etiologies of organ system pathologies

Head circumference is normal at birth, indicating that it is not a developmental disorder, or due to premature failure of neural development, disordered neuronal migration, or grossly aberrant connectivity. CS is likely a heterogeneous disease, with different pathologies such as dysmyelination, demyelination, calcification, vasculopathy and ischemia possibly playing roles (Demaerel et al., 1992; Koob et al., 2010; Rapin et al., 2006; Weidenheim et al., 2009). Cell loss and demyelination lead to a variety of clinical manifestations across different systems - sensorineural hearing loss, pigmentary retinopathy, optic disk pallor, peripheral neuropathy, white matter loss, cerebellar atrophy, etc. Pathological findings typical of Alzheimer’s dementia are not seen, although there are reports of ubiquitin reactivity of axons, a feature also seen in aging (Dickson et al., 1990; Rapin et al., 2006; Weidenheim et al., 2009). Proliferation of astrocytes is often seen, but there are no areas of inflammation in areas of white matter pathology which could cause the reactive astrocytosis.

Endocrine function appears to be normal, and not a cause of the many clinical features seen in CS (Table 1). The pituitary and thyroid are well developed, and no deficiencies of growth

hormone or thyroid stimulating hormone have been reported. Calcium and phosphorus levels are normal, and cannot explain the dystrophic calcification (Inoue et al., 1997; Sugarman et al., 1977; Wilson et al., 2015). Secondary sexual maturation characteristics usually appear at the appropriate ages, and there is at least one instance of a female patient with CS successfully giving birth (Lahiri and Davies, 2003).

While calcifications may be seen in the basal ganglia as part of normal aging (Cohen et al., 1980; Fénelon et al., 1993; Heron et al., 1999; Selekler, 1982), the severity and extent of calcifications in CS is qualitatively and quantitatively different. Certain congenital viral infections have been associated with severe brain calcification, but there is no evidence at the current time of such an etiology in CS patients. The most affected neurons are in the basal ganglia. These neurons have high oxygen requirements, which could implicate mitochondrial pathology. There is also severe neuronal loss in the hippocampus (Leech et al., 1985), another high oxygen requirement area (Mintun et al., 2001). Oxygen consumption and ROS activity is, however, also important for neuronal functions such as neurogenesis (Le Belle et al., 2011), so this may be a more complex scenario. In the cortex, neuronal loss was more in the depths of the sulci, again suggesting hypoxic ischemic injury. The number of capillaries is increased around the calcified foci in the basal ganglia (Rapin, 2013).

Lipid peroxidation and protein glycation markers were found in the perivascular calcification areas in the globus pallidus and cerebellum more predominantly in CS than XP-A patients (Hayashi et al., 2005; Lindenbaum et al., 2001; Rapin et al., 2000). Similar calcification is seen in Aicardi-Goutieres syndrome (Livingston et al., 2014, 2013; Mizuno et al., 2011; Piana et al., 2016; Ramantani et al., 2010), which has vasculopathy. Calcification is seen in the leptomeningeal vessels (Rapin et al., 2006; Weidenheim et al., 2009), which raises the chicken-and-egg conundrum – did calcification lead to vascular damage, or was vascular damage and resulting hypoxia the reason for the calcification.

Also supporting a vascular-hypoxia theory is the fact that there is relative preservation of myelin in perivascular areas. Increased numbers of small arteries and arterioles that were filled with fibrotic tissue, and small twisted and longitudinally running capillaries in the cerebral white matter (“string vessels”) have been observed in areas of leukodystrophy (Rapin et al., 2006). Large and medium sized systemic arteries may show marked atherosclerosis (Hayashi et al., 2012), which may even lead to cerebral infarctions, especially in the later stages.

3.1 Diagnostic criteria – classical and modified

Diagnosis is made either by the typical phenotype (Table 4), or by specific tests for DNA repair which measure the recovery of RNA transcription after exposure to UV radiation (Mayne and Lehmann, 1982; Stefanini et al., 1996). This is based on the notion that CS is defective in transcription-coupled nucleotide excision DNA repair. Next generation sequencing has recently been included as a diagnostic tool (Laugel, 1993).

3.2 Testing and treatment

A variety of screening tests are recommended in CS patients (Table 5). These include annual eye exams with fundoscopy and evaluation for cataracts. Visual evoked potentials may be considered to accurately document retinal function. Hearing tests on an annual basis are also recommended. This can be done with pure tone and behavioral audiometry tests, but in individuals in whom this might be difficult, brainstem evoked potentials might be considered, although it may necessitate sedation. Periodic evaluation of renal and liver function tests are recommended, as are regular blood pressure and blood glucose testing (Kubota et al., 2015; Wilson et al., 2015); many individuals with CS may have abnormal glucose metabolism (Wilson et al., 2015).

Physical therapy, cochlear implants for hearing, cataract surgeries, sunscreen for photosensitivity, feeding tubes for malnutrition, etc. may be helpful if indicated. At the current time, only symptomatic treatment is available, and no treatments have been identified which could slow or halt the progression of the disease. Mean age of death is approximately 12 years (Kubota et al., 2015; Nance and Berry, 1992; Rapin, 2013; Wilson et al., 2010).

4.1 Genetics

CS is an autosomal recessive disorder. CS has been classified into mainly 2 different complementation groups: 1) CSA, due to a mutation on ERCC8 on chromosome 5q12–q31, and 2) CSB, due to a mutation on ERCC6 on chromosome 10q11. CSB accounts for about 70–75 percent of CS cases (Laugel, 2013; Natale, 2011).

Based on the severity of clinical features, CS patients present with a continuous spectrum of clinical features. Although historically CS was classified into type 1, 2 and 3, there is an emerging hypothesis that there is no clear distinction between the different types. Type 1 is the classical type, with onset of symptoms in early childhood, usually after 1 year of age. Type 2 involves much more severe symptoms and often presents at birth. Type 3 is the mildest, and usually appears later in childhood (Laugel, 2013; Nance and Berry, 1992). CSA genotype is predominantly composed of the CS1 phenotype, and the CSB genotypes are predominantly composed of the CS2 phenotype (Laugel, 2013).

CS patients with mutations in XPB (ERCC3), XPD (ERCC2) and XPG genes have the unfortunate combination of severe photosensitivity and increased skin cancer risk of XP patients, along with the severe somatic and neurologic manifestations of CS patients. COFS is considered to be a particularly severe variant of CS, due to mutations in CSB. Ultraviolet sensitivity syndrome (UVSS) is considered to be part of the spectrum of CS, and has mild features, mainly photosensitivity.

4.2 Molecular mechanisms – current models

CS has traditionally been thought of as a disorder caused by defective transcription and transcription-coupled nucleotide excision repair (TC-NER)(Mayne and Lehmann, 1982; Troelstra et al., 1992). Defective DNA repair stalls RNA polymerase transcription, and the CSB protein is believed to assist RNA polymerases in dealing with transcription blocks

caused by DNA damage, and then in recruiting nucleotide excision repair proteins to remove the damage (Aamann et al., 2013). In addition, CSB itself is a transcription factor of significant importance (Kristensen et al., 2013). There is delayed recovery of DNA repair after irradiation of skin fibroblasts from these patients with UV light (Lehmann et al., 1979; Lindenbaum et al., 2001; Rapin et al., 2000; Stefanini et al., 1996). As such, CS has been grouped with other disorders with defective NER such as xeroderma pigmentosum and trichothiodystrophy. However, CS is not associated with a high cancer incidence, which is usually seen in the DNA repair deficient syndromes (Lehmann, 2003). The lack of carcinogenicity in CS might be due to inhibition of cellular growth because of increased apoptosis of DNA damaged cells (Caputo et al., 2013), but it remains an interesting and unresolved question to understand why CS stads out as not being associated with increased cancer.

Many aspects of CS cannot be explained by deficient NER. A variety of diseases – UV skin sensitivity syndrome (UVSS), the various complementation groups of xeroderma pigmentosum (XP), COFS, and trichothiodystrophy (TTD) have defective TC-NER. Their clinical features vary widely. For example, XP has approximately a ten-thousand fold increased risk of non-melanoma skin cancers (Bradford et al., 2011) and a tenfold risk of CNS tumors, which are not found in CS (Brooks et al., 2008; Kraemer et al., 2007; Lehmann, 2003). Thus, we have a spectrum of disorders in humans and mouse models which cannot all be explained with defective TC-NER.

4.3 Molecular functions and cellular physiology of CSA and CSB

CSB does not have helicase activity (Berquist and Wilson, 2009), but is able to anneal complementary DNA strands (Berquist and Wilson, 2009). The exact role of the ATPase activity of CSB is not known, but it may be necessary for nucleosome remodeling (Cho et al., 2013; Citterio et al., 2000). Interestingly, CSB ATPase has been found to have a particularly strong functional interaction with the mitochondrial transcription factor TFAM (Berquist et al., 2012), and this may reflect an important biological function of CSB inside mitochondria on DNA metabolism. CSB is also important in various forms of DNA repair including base excision repair (Stevnsner et al., 2008), inter-strand crosslink repair (Enoiu et al., 2012; Iyama et al., 2015) and DNA double-strand break repair (Batenburg et al., 2015; Wei et al., 2015).

The roles of CSB in NER has been covered in recent reviews (Marteijn et al., 2014) and thus will not be detailed here. Other reviews (McKinnon, 2009) have discussed how aspects of CSB function in NER can account for neurodegenerative features. The role of CSB in base excision repair (Aamann et al., 2013) may be more significant in the generation of neurodegeneration than its role in NER since the main DNA damage accumulation in the brain is oxidative, However, in this review we are focusing mainly on the mitochondrial changes in CSB.

CSA is a WD40 repeat protein. It functions as an adaptor protein in an E3-ubiquitin ligase complex. The crystal structure of CSA in complex with DDB1,Cul4 and Rbx1 has been solved (Fischer et al., 2011). CSA may be involved in the targeted ubiquitination of proteins

such as CSB or RNA polymerase II (Fischer et al., 2011; Fousteri et al., 2006). CSA is activated by stalled RNA polymerases in a CSB-dependent manner (Fousteri et al., 2006).

Alterations in mitochondrial function have been found in cells from CS patients (Chatre et al., 2015; Cleaver et al., 2014; Osenbroch et al., 2009; Pascucci et al., 2012; Scheibye-Knudsen et al., 2012). CSB has important functions in stimulating mitochondrial DNA repair (Aamann et al., 2010; Kamenisch et al., 2010; Stevnsner et al., 2002), stimulating mitochondrial transcription (Berquist et al., 2012), and regulating mitochondrial proteostasis (Chatre et al., 2015). Impairment of these functions could contribute to the alterations in mitochondrial functions found in the cells of CS patients.

In addition, mitochondrial changes may be due to nuclear mitochondrial signaling from nuclear DNA damage, possibly via the DNA repair enzyme poly-ADP-ribose polymerase 1 (PARP1) (Fang et al., 2014; Scheibye-Knudsen et al., 2014b). An accumulation of DNA damage could lead to activation of PARP1 and loss of NAD^+, the substrate for PARP1 (Cantó et al., 2012; Fang et al., 2014; Scheibye-Knudsen et al., 2014a). NAD^+ regulates the activity of a number of other proteins such as the sirtuin family of protein deacetylases, leading to changes in mitochondrial signaling pathways, for example viaPGC-1 α (Scheibye-Knudsen et al., 2015). Depletion of NAD^+ can lead to decreased activity of sirtuins, including the mitochondrial sirtuin SIRT3, which may impair the ability of cells to deal with various biological stresses, including states of calcium overload. This could also lead to dystrophic calcification (Cheng et al., 2016a). Supporting evidence for this pathway comes from observations that treatments with PARP1 inhibitors or NAD^+ precursors rescued some features in a mouse model of CS (Scheibye-Knudsen et al., 2014b).

4.4 CS resembles mitochondrial diseases

The clinical manifestations of CS resemble those of mitochondrial diseases. Utilizing the MITODB database tool (www.mitodb.com), CS qualifies as a mitochondrial disease (Scheibye-Knudsen et al., 2013) (Figure 5). Mitochondrial diseases are usually multisystem diseases, characterized by the presence of ataxia, seizures, myopathy, hearing loss, neuropathy, failure to thrive, cerebellar atrophy, mental retardation, cerebral atrophy, basal ganglia pathology and leukodystrophy (Scheibye-Knudsen et al., 2015) - all features found in CS.

Many of the clinical features seen in CS are also observed in mitochondrial disorders. Kearns-Sayre syndrome has a pigmentary retinopathy which is very similar to that seen in CS. Leber's hereditary optic neuropathy has, as the name implies, severe optic neuropathy, not dissimilar to the optic atrophy noted in CS. Leigh syndrome presents in infancy or early childhood, and many individuals with this disease have lactic acidosis and peripheral neuropathy. Stroke like episodes, short stature and dementia are found in mitochondrial encephalopathy with lactic acidosis and stroke like episodes (MELAS). Myoclonic epilepsy with ragged red fibers (MERRF) has a pigmentary retinopathy very similar to that seen in CS. Lactic acidosis is a very common feature of mitochondrial disorders in general, occurring in more than 40 percent of the classical mitochondrial diseases(Scheibye-Knudsen et al., 2015). This feature was also observed in the brain of Csb mice (Scheibye-Knudsen et al., 2014b) and in CS patients (Koob et al., 2010).

Additionally, mitochondrial dysfunction has been shown to be important in many of the clinical features seen in CS individuals, such as basal ganglia calcification (Finsterer and Kopsa, 2005), sensorineural hearing loss (Han and Someya, 2013; Someya and Prolla, 2010),optic atrophy (Lascaratos et al., 2015), retinal degeneration (Mao et al., 2014), and vascular calcification and atherosclerosis (Kim et al., 2012; Lee et al., 2015; Villa-Bellosta et al., 2013; Yu et al., 2013). Mitochondrial dysfunction also has important roles in neurodegeneration (Calì et al., 2012; Cheng et al., 2016b; Krols et al., 2016), that could be mediated through other neurotrophic factors such as brain-derived neurotrophic factor (Su et al., 2014). Recently, treatment with brain-derived neurotrophic factor was shown to overcome at least some of the neuritogenesis defects in CS cell lines (Wang et al., 2016).

4.5 Animal models of Cockayne syndrome

4.5.1 Mouse models of Cockayne syndrome—The first CS mouse model was generated by introducing the same truncation mutation seen in the CS1AN patient into the murine Csb gene ($Csb^{m/m}$)(van der Horst et al., 1997). Such mice recapitulated aspects of human CS, such as motor dysfunction and cachectic dwarfism (Scheibye-Knudsen et al., 2014b, 2012). However, the mouse also showed increased susceptibility to UV induced skin cancer, a feature generally seen in xeroderma pigmentosum but not in CS (Kraemer et al., 2007). The $Csb^{m/m}$mice also demonstrated loss of cells in the retina (Gorgels et al., 2007) and sensorineural hearing loss (Scheibye-Knudsen et al., 2014b, 2012), a finding that was later repeated in a second study (Nagtegaal et al., 2015). The $Csb^{m/m}$ mice also displayed increased lactate production (Cantó et al., 2012; Koob et al., 2010). However, no additional major neurodegenerative features were observed in the mouse model, raising the possibility that the $Csb^{m/m}$ mice represent mild cases of CS (Scheibye-Knudsen et al., 2012). The overall findings seen in $Csb^{m/m}$ mice were also seen in a mouse model where murine Csa had been knocked out (van der Horst et al., 2002).

Crossing the $Csb^{m/m}$or $Csa^{-/-}$ mice with mice deficient in genes coding for other members of the nucleotide excision repair machinery, such as $xpc^{-/-}$ or $xpa^{-/-}$ mice, does, however, led to profound neurodegeneration and early death (Brace et al., 2013; Jaarsma et al., 2011; Laposa et al., 2007). Most exciting, though, are the recent findings suggesting that some molecular interventions may be able to alleviate the neurodegenerative features of mouse and nematode models of CS (Brace et al., 2013; Scheibye-Knudsen et al., 2014b).

4.5.2 Nematode models of CS—In addition to mouse models for CS, nematode models have emerged that can help us understand the disease better. *C. elegans* was originally introduced as a model organism by Sydney Brenner to study development and neurobiology (Brenner, 1974), and has since been established as a powerful model to study diverse biological processes including aging mechanisms.

There are several advantages to using *C. elegans* as a model to study aging and CS. They have a relatively short lifespan of 2–3 weeks, making it feasible to perform life span studies. They are easy to grow inexpensively in large quantities. In addition to life span assays, health span can be analyzed. This includes pharyngeal pumping, which is an important function necessary for food intake (Klass, 1983). Memory can be analyzed in *C. elegans*

models using well developed chemotactic assays (Kauffman et al., 2011) that allow for measuring short and long term associated memory and is very informative (Kauffman et al., 2011). The worms are easy to maintain and ideal for high throughput genetic screening.

Adult *C. elegans* have several distinct tissue types including epithelial, intestinal, muscular and neuronal tissue, as well as germ line cells undergoing meiosis, thus making it possible to observe the effect of mutations on a variety of cell types. In addition, approximately 83% of the *C. elegans* proteome shares homology to human genes (Lai et al., 2000), and specific RNAi knockdown mutants can be generated. This has led to the identification of several genetic pathways regulating a variety of physiological processes, including pathways that regulate aging (Chen et al., 2015; Cutler et al., 2014; Hyun et al., 2008a; Iser and Wolkow, 2007; Kenyon, 2010; Love et al., 2010; Rangaraju et al., 2015; Stroustrup et al., 2016).

Both the GGR (global genomic repair) and TC-NER branches of the NER pathway are evolutionarily conserved in *C. elegans* (Lans et al., 2010; Meyer et al., 2007) and NER activity has been associated with aging in *C. elegans* (Hyun et al., 2008b; Meyer et al., 2007; Murakami and Johnson, 1996). *Csa-1*(Babu et al., 2014) and *csb-1*(Lans et al., 2010) function specifically in the TC-NER pathway similar to their human counterparts (Fousteri and Mullenders, 2008). *Csa-1* mutant L1 larvae exhibited increased sensitivity to UV radiation compared to wildtype worms, and this sensitivity was enhanced in worms with defective GGR (Babu et al., 2014). Lee and coworkers observed increased sensitivity to UV radiation when *csb-1* was depleted via RNAi interference (Lee et al., 2002). *Csb-1* knockdown worms also demonstrated defective germline development, defective proliferation and embryogenesis in the presence of UV radiation, indicating a role for *csb-1* in the NER pathway. Increased sensitivity to UV radiation seen when *csa-1* or *csb-1* was defective resembles the UV photosensitivity seen in CS patients. These studies indicate that the nucleotide excision repair pathway is conserved in *C. elegans* and that *csa-1* and *csb-1* are functional homologs to human *CSA* and *CSB* genes. Furthermore, these studies validate *C. elegans* as a useful model to study UV-induced DNA damage and repair.

In addition to the above mentioned model systems it would also be very important to use human systems, for example, oligodendrocytic or neural lineages from CS individuals or mouse models. Postmortem material has been widely used in studies on other pathologies such as Alzheimers and could be informative for functional and histiological analysis.

6.0 Conclusion

CS exhibits many of the features of normal human aging, such as the skin changes, loss of subcutaneous fat, stooped posture, cataracts and the advanced atherosclerotic changes. It resembles NER disorders in some aspects such as the cutaneous photosensitivity, but differs with respect to the severe degeneration of the nervous system. NER defects are insufficient to explain the clinical features of CS, and a mitochondrial pathology may be more likely as the underlying cause. Mitochondrial pathology underlies many of the features of normal aging. Most excitingly, amelioration of some features and increasing health span might be possible by measures which elevate NAD^+ and improve mitochondrial health.

Acknowledgments

This work was supported by the Intramural Research Program of the NIH, National Institute on Aging. We would like to thank Dr. Nazir Okur and Tyler Golato for critically reading the manuscript.

References

Aamann MD, Muftuoglu M, Bohr VA, Stevnsner T. Multiple interaction partners for Cockayne syndrome proteins: implications for genome and transcriptome maintenance. Mech Ageing Dev. 2013; 134:212–224. DOI: 10.1016/j.mad.2013.03.009 [PubMed: 23583689]

Aamann MD, Sorensen MM, Hvitby C, Berquist BR, Muftuoglu M, Tian J, de Souza-Pinto NC, Scheibye-Knudsen M, Wilson DM, Stevnsner T, Bohr VA. Cockayne syndrome group B protein promotes mitochondrial DNA stability by supporting the DNA repair association with the mitochondrial membrane. FASEB J. 2010; 24:2334–2346. DOI: 10.1096/fj.09-147991 [PubMed: 20181933]

Babu V, Hofmann K, Schumacher B. A C. elegans homolog of the Cockayne syndrome complementation group A gene. DNA Repair. 2014; 24:57–62. DOI: 10.1016/j.dnarep.2014.09.011 [PubMed: 25453470]

Bartenjev I, Butina MR, Potocnik M. Rare case of Cockayne syndrome with xeroderma pigmentosum. Acta Derm Venereol. 2000; 80:213–214. [PubMed: 10954218]

Batenburg NL, Thompson EL, Hendrickson EA, Zhu XD. Cockayne syndrome group B protein regulates DNA double-strand break repair and checkpoint activation. EMBO J. 2015; 34:1399–1416. DOI: 10.15252/embj.201490041 [PubMed: 25820262]

Berquist BR, Canugovi C, Sykora P, Wilson DM, Bohr VA. Human Cockayne syndrome B protein reciprocally communicates with mitochondrial proteins and promotes transcriptional elongation. Nucleic Acids Res. 2012; 40:8392–8405. DOI: 10.1093/nar/gks565 [PubMed: 22743267]

Berquist BR, Wilson DM. Nucleic acid binding activity of human Cockayne syndrome B protein and identification of Ca(2+) as a novel metal cofactor. J Mol Biol. 2009; 391:820–832. DOI: 10.1016/j.jmb.2009.06.078 [PubMed: 19580815]

Boltshauser E, Yalcinkaya C, Wichmann W, Reutter F, Prader A, Valavanis A. MRI in Cockayne syndrome type I. Neuroradiology. 1989; 31:276–277. [PubMed: 2779780]

Brace LE, Vose SC, Vargas DF, Zhao S, Wang XP, Mitchell JR. Lifespan extension by dietary intervention in a mouse model of Cockayne syndrome uncouples early postnatal development from segmental progeria. Aging Cell. 2013; 12:1144–1147. DOI: 10.1111/acel.12142 [PubMed: 23895664]

Bradford PT, Goldstein AM, Tamura D, Khan SG, Ueda T, Boyle J, Oh KS, Imoto K, Inui H, Moriwaki SI, Emmert S, Pike KM, Raziuddin A, Plona TM, DiGiovanna JJ, Tucker MA, Kraemer KH. Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. J Med Genet. 2011; 48:168–176. DOI: 10.1136/jmg.2010.083022 [PubMed: 21097776]

Brenner S. The genetics of Caenorhabditis elegans. Genetics. 1974; 77:71–94. [PubMed: 4366476]

Brooks PJ. Blinded by the UV light: How the focus on transcription-coupled NER has distracted from understanding the mechanisms of Cockayne syndrome neurologic disease. DNA Repair. 2013; 12:656–671. DOI: 10.1016/j.dnarep.2013.04.018 [PubMed: 23683874]

Brooks PJ, Cheng TF, Cooper L. Do all of the neurologic diseases in patients with DNA repair gene mutations result from the accumulation of DNA damage? DNA Repair. 2008; 7:834–848. DOI: 10.1016/j.dnarep.2008.01.017 [PubMed: 18339586]

Calì T, Ottolini D, Brini M. Mitochondrial Ca2+ and neurodegeneration. Cell Calcium. 2012; 52:73–85. DOI: 10.1016/j.ceca.2012.04.015 [PubMed: 22608276]

Campistol Plana J, Riverola de Veciana A, Poo Argüelles P, Colomer Oferil J, Moreno Hernández J. Peripheral neuropathy as a presenting form of Cockayne syndrome. Arch Neurobiol. 1991; 54:141–145.

Cantó C, Houtkooper RH, Pirinen E, Youn DY, Oosterveer MH, Cen Y, Fernandez-Marcos PJ, Yamamoto H, Andreux PA, Cettour-Rose P, Gademann K, Rinsch C, Schoonjans K, Sauve AA,

Auwerx J. The NAD+ Precursor Nicotinamide Riboside Enhances Oxidative Metabolism and Protects against High-Fat Diet-Induced Obesity. Cell Metab. 2012; 15:838–847. DOI: 10.1016/j.cmet.2012.04.022 [PubMed: 22682224]

Caputo M, Frontini M, Velez-Cruz R, Nicolai S, Prantera G, Proietti-De-Santis L. The CSB repair factor is overexpressed in cancer cells, increases apoptotic resistance, and promotes tumor growth. DNA Repair. 2013; 12:293–299. DOI: 10.1016/j.dnarep.2013.01.008 [PubMed: 23419237]

Cataracts | National Eye Institute, n.d.

Chatre L, Biard DSF, Sarasin A, Ricchetti M. Reversal of mitochondrial defects with CSB-dependent serine protease inhibitors in patient cells of the progeroid Cockayne syndrome. Proc Natl Acad Sci U S A. 2015; 112:E2910–E2919. DOI: 10.1073/pnas.1422264112 [PubMed: 26038566]

Chen ATY, Guo C, Itani OA, Budaitis BG, Williams TW, Hopkins CE, McEachin RC, Pande M, Grant AR, Yoshina S, Mitani S, Hu PJ. Longevity Genes Revealed by Integrative Analysis of Isoform-Specific daf-16/FoxO Mutants of Caenorhabditis elegans. Genetics. 2015; 201:613–629. DOI: 10.1534/genetics.115.177998 [PubMed: 26219299]

Cheng A, Yang Y, Zhou Y, Maharana C, Lu D, Peng W, Liu Y, Wan R, Marosi K, Misiak M, Bohr VA, Mattson MP. Mitochondrial SIRT3 Mediates Adaptive Responses of Neurons to Exercise and Metabolic and Excitatory Challenges. Cell Metab. 2016a; 23:128–142. DOI: 10.1016/j.cmet.2015.10.013 [PubMed: 26698917]

Cheng A, Yang Y, Zhou Y, Maharana C, Lu D, Peng W, Liu Y, Wan R, Marosi K, Misiak M, Bohr VA, Mattson MP. Mitochondrial SIRT3 Mediates Adaptive Responses of Neurons to Exercise and Metabolic and Excitatory Challenges. Cell Metab. 2016b; 23:128–142. DOI: 10.1016/j.cmet.2015.10.013 [PubMed: 26698917]

Cho I, Tsai PF, Lake RJ, Basheer A, Fan HY. ATP-dependent chromatin remodeling by Cockayne syndrome protein B and NAP1-like histone chaperones is required for efficient transcription-coupled DNA repair. PLoS Genet. 2013; 9:e1003407.doi: 10.1371/journal.pgen.1003407 [PubMed: 23637612]

Choong CS, Liew KL, Huang YF, Chiu PC, Hsieh KS. Cockayne syndrome with tetralogy of Fallot: a case report. Zhonghua Yi Xue Za Zhi Chin. Med J Free China Ed. 1997; 59:199–203.

Citterio E, Van Den Boom V, Schnitzler G, Kanaar R, Bonte E, Kingston RE, Hoeijmakers JH, Vermeulen W. ATP-dependent chromatin remodeling by the Cockayne syndrome B DNA repair-transcription-coupling factor. Mol Cell Biol. 2000; 20:7643–7653. [PubMed: 11003660]

Cleaver JE, Brennan-Minnella AM, Swanson RA, Fong K, Chen J, Chou K, Chen Y, Revet I, Bezrookove V. Mitochondrial reactive oxygen species are scavenged by Cockayne syndrome B protein in human fibroblasts without nuclear DNA damage. Proc Natl Acad Sci U S A. 2014; 111:13487–13492. DOI: 10.1073/pnas.1414135111 [PubMed: 25136123]

Cockayne EA. Dwarfism with Retinal Atrophy and Deafness. Arch Dis Child. 1946; 21:52–54.

Cockayne EA. Dwarfism with retinal atrophy and deafness. Arch Dis Child. 1936; 11:1–8. DOI: 10.1136/adc.11.61.1 [PubMed: 21032019]

Cohen CR, Duchesneau PM, Weinstein MA. Calcification of the basal ganglia as visualized by computed tomography. Radiology. 1980; 134:97–99. DOI: 10.1148/radiology.134.1.7350641 [PubMed: 7350641]

Coles WH. Ocular manifestations of Cockayne's syndrome. Am J Ophthalmol. 1969; 67:762–764. [PubMed: 5769811]

Crome L, Kanjilal GC. Cockayne's syndrome: case report. J Neurol Neurosurg Psychiatry. 1971; 34:171–178. [PubMed: 4999043]

Cutler RG, Thompson KW, Camandola S, Mack KT, Mattson MP. Sphingolipid metabolism regulates development and lifespan in Caenorhabditis elegans. Mech Ageing Dev. 2014; :143–144. DOI: 10.1016/j.mad.2014.11.002

Demaerel P, Kendall BE, Kingsley D. Cranial CT and MRI in diseases with DNA repair defects. Neuroradiology. 1992; 34:117–121. [PubMed: 1603308]

Demaerel P, Wilms G, Verdru P, Carton H, Baert AL. MRI in the diagnosis of Cockayne's syndrome. One case. J Neuroradiol J Neuroradiol. 1990; 17:157–160. [PubMed: 2250182]

Dickson DW, Wertkin A, Kress Y, Ksiezak-Reding H, Yen SH. Ubiquitin immunoreactive structures in normal human brains. Distribution and developmental aspects. Lab Investig J Tech Methods Pathol. 1990; 63:87–99.

Dollfus H, Porto F, Caussade P, Speeg-Schatz C, Sahel J, Grosshans E, Flament J, Sarasin A. Ocular Manifestations in the Inherited DNA Repair Disorders. Surv Ophthalmol. 2003; 48:107–122. DOI: 10.1016/S0039-6257(02)00400-9 [PubMed: 12559331]

Enoiu M, Jiricny J, Schärer OD. Repair of cisplatin-induced DNA interstrand crosslinks by a replication-independent pathway involving transcription-coupled repair and translesion synthesis. Nucleic Acids Res. 2012; 40:8953–8964. DOI: 10.1093/nar/gks670 [PubMed: 22810206]

Fang EF, Scheibye-Knudsen M, Brace LE, Kassahun H, SenGupta T, Nilsen H, Mitchell JR, Croteau DL, Bohr VA. Defective mitophagy in XPA via PARP-1 hyperactivation and NAD(+)/SIRT1 reduction. Cell. 2014; 157:882–896. DOI: 10.1016/j.cell.2014.03.026 [PubMed: 24813611]

Fénelon G, Gray F, Paillard F, Thibierge M, Mahieux F, Guillani A. A prospective study of patients with CT detected pallidal calcifications. J Neurol Neurosurg Psychiatry. 1993; 56:622–625. DOI: 10.1136/jnnp.56.6.622 [PubMed: 8509774]

Finsterer J, Kopsa W. Basal Ganglia Calcification in Mitochondrial Disorders. Metab Brain Dis. 2005; 20:219–226. DOI: 10.1007/s11011-005-7209-9 [PubMed: 16167199]

Fischer ES, Scrima A, Böhm K, Matsumoto S, Lingaraju GM, Faty M, Yasuda T, Cavadini S, Wakasugi M, Hanaoka F, Iwai S, Gut H, Sugasawa K, Thomä NH. The molecular basis of CRL4DDB2/CSA ubiquitin ligase architecture, targeting, and activation. Cell. 2011; 147:1024–1039. DOI: 10.1016/j.cell.2011.10.035 [PubMed: 22118460]

Fousteri M, Mullenders LHF. Transcription-coupled nucleotide excision repair in mammalian cells: molecular mechanisms and biological effects. Cell Res. 2008; 18:73–84. DOI: 10.1038/cr.2008.6 [PubMed: 18166977]

Fousteri M, Vermeulen W, van Zeeland AA, Mullenders LHF. Cockayne syndrome A and B proteins differentially regulate recruitment of chromatin remodeling and repair factors to stalled RNA polymerase II in vivo. Mol Cell. 2006; 23:471–482. DOI: 10.1016/j.molcel.2006.06.029 [PubMed: 16916636]

Fujimoto WY, Green ML, Seegmiller JE. Cockayne's syndrome: report of a case with hyperlipoproteinemia, hyperinsulinemia, renal disease, and normal growth hormone. J Pediatr. 1969; 75:881–884. [PubMed: 5357933]

Funaki S, Takahashi S, Murakami H, Harada K, Kitamura H. Cockayne syndrome with recurrent acute tubulointerstitial nephritis. Pathol Int. 2006; 56:678–682. DOI: 10.1111/j.1440-1827.2006.02029.x [PubMed: 17040291]

Gandolfi A, Horoupian D, Rapin I, Deteresa R, Hyams V. Deafness in Cockayne's syndrome: Morphological, morphometric, and quantitative study of the auditory pathway. Ann Neurol. 1984; 15:135–143. DOI: 10.1002/ana.410150205 [PubMed: 6703654]

Gorgels TGMF, van der Pluijm I, Brandt RMC, Garinis GA, van Steeg H, van den Aardweg G, Jansen GH, Ruijter JM, Bergen AAB, van Norren D, Hoeijmakers JHJ, van der Horst GTJ. Retinal Degeneration and Ionizing Radiation Hypersensitivity in a Mouse Model for Cockayne Syndrome. Mol Cell Biol. 2007; 27:1433–1441. DOI: 10.1128/MCB.01037-06 [PubMed: 17145777]

Grunnet ML, Zimmerman AW, Lewis RA. Ultrastructure and electrodiagnosis of peripheral neuropathy in Cockayne's syndrome. Neurology. 1983; 33:1606–1609. [PubMed: 6316205]

Hamel C. Retinitis pigmentosa. Orphanet J Rare Dis. 2006; 1:40.doi: 10.1186/1750-1172-1-40 [PubMed: 17032466]

Han C, Someya S. Mouse Models of Age-related Mitochondrial Neurosensory Hearing Loss. Mol Cell Neurosci. 2013; 55:95–100. DOI: 10.1016/j.mcn.2012.07.004 [PubMed: 22820179]

Hayashi M, Araki S, Kohyama J, Shioda K, Fukatsu R. Oxidative nucleotide damage and superoxide dismutase expression in the brains of xeroderma pigmentosum group A and Cockayne syndrome. Brain Dev. 2005; 27:34–38. DOI: 10.1016/j.braindev.2004.04.001 [PubMed: 15626539]

Hayashi M, Itoh M, Araki S, Kumada S, Shioda K, Tamagawa K, Mizutani T, Morimatsu Y, Minagawa M, Oda M. Oxidative Stress and Disturbed Glutamate Transport in Hereditary Nucleotide Repair Disorders. J Neuropathol Exp Neurol. 2001; 60:350–356. DOI: 10.1093/jnen/60.4.350 [PubMed: 11305870]

Hayashi M, Miwa-Saito N, Tanuma N, Kubota M. Brain vascular changes in Cockayne syndrome. Neuropathology. 2012; 32:113–117. DOI: 10.1111/j.1440-1789.2011.01241.x [PubMed: 21749465]

Heron E, Hernigou A, Chatellier G, Fornes P, Emmerich J, Fiessinger JN. Intracerebral Calcification in Systemic Sclerosis. Stroke. 1999; 30:2183–2185. DOI: 10.1161/01.STR.30.10.2183 [PubMed: 10512926]

Higginbottom MC, Griswold WR, Jones KL, Vasquez MD, Mendoza SA, Wilson CB. The Cockayne syndrome: an evaluation of hypertension and studies of renal pathology. Pediatrics. 1979; 64:929–934. [PubMed: 514720]

Hirooka M, Hirota M, Kamada M. Renal lesions in Cockayne syndrome. Pediatr Nephrol Berl Ger. 1988; 2:239–243.

Hyun M, Lee J, Lee K, May A, Bohr VA, Ahn B. Longevity and resistance to stress correlate with DNA repair capacity in Caenorhabditis elegans. Nucleic Acids Res. 2008a; 36:1380–1389. DOI: 10.1093/nar/gkm1161 [PubMed: 18203746]

Hyun M, Lee J, Lee K, May A, Bohr VA, Ahn B. Longevity and resistance to stress correlate with DNA repair capacity in Caenorhabditis elegans. Nucleic Acids Res. 2008b; 36:1380–1389. DOI: 10.1093/nar/gkm1161 [PubMed: 18203746]

Inoue T, Sano N, Ito Y, Matsuzaki Y, Okauchi Y, Kondo H, Horiuchi N, Nakao K, Iwata M. An Adult Case of Cockayne Syndrome without Sclerotic Angiopathy. Intern Med. 1997; 36:565–570. DOI: 10.2169/internalmedicine.36.565 [PubMed: 9260774]

Iser WB, Wolkow CA. DAF-2/insulin-like signaling in C. elegans modifies effects of dietary restriction and nutrient stress on aging, stress and growth. PloS One. 2007; 2:e1240.doi: 10.1371/journal.pone.0001240 [PubMed: 18043747]

Itoh M, Hayashi M, Shioda K, Minagawa M, Isa F, Tamagawa K, Morimatsu Y, Oda M. Neurodegeneration in hereditary nucleotide repair disorders. Brain Dev. 1999; 21:326–333. DOI: 10.1016/S0387-7604(99)00033-9 [PubMed: 10413020]

Iwasaki S, Kaga K. Chronological changes of auditory brainstem responses in Cockayne's syndrome. Int J Pediatr Otorhinolaryngol. 1994; 30:211–221. [PubMed: 7836034]

Iyama T, Lee SY, Berquist BR, Gileadi O, Bohr VA, Seidman MM, McHugh PJ, Wilson DM. CSB interacts with SNM1A and promotes DNA interstrand crosslink processing. Nucleic Acids Res. 2015; 43:247–258. DOI: 10.1093/nar/gku1279 [PubMed: 25505141]

Jaarsma D, van der Pluijm I, de Waard MC, Haasdijk ED, Brandt R, Vermeij M, Rijksen Y, Maas A, van Steeg H, Hoeijmakers JHJ, van der Horst GTJ. Age-related neuronal degeneration: complementary roles of nucleotide excision repair and transcription-coupled repair in preventing neuropathology. PLoS Genet. 2011; 7:e1002405.doi: 10.1371/journal.pgen.1002405 [PubMed: 22174697]

Jin K, Handa T, Ishihara T, Yoshii F. Cockayne syndrome: report of two siblings and review of literature in Japan. Brain Dev. 1979; 1:305–312. [PubMed: 553450]

Kamenisch Y, Fousteri M, Knoch J, von Thaler AK, Fehrenbacher B, Kato H, Becker T, Dollé MET, Kuiper R, Majora M, Schaller M, van der Horst GTJ, van Steeg H, Röcken M, Rapaport D, Krutmann J, Mullenders LH, Berneburg M. Proteins of nucleotide and base excision repair pathways interact in mitochondria to protect from loss of subcutaneous fat, a hallmark of aging. J Exp Med. 2010; 207:379–390. DOI: 10.1084/jem.20091834 [PubMed: 20100872]

Kauffman A, Parsons L, Stein G, Wills A, Kaletsky R, Murphy C. C. elegans Positive Butanone Learning, Short-term, and Long-term Associative Memory Assays. J Vis Exp JoVE. 2011; doi: 10.3791/2490

Kenyon CJ. The genetics of ageing. Nature. 2010; 464:504–512. DOI: 10.1038/nature08980 [PubMed: 20336132]

Kim H, Kim HJ, Lee K, Kim JM, Kim HS, Kim JR, Ha CM, Choi YK, Lee SJ, Kim JY, Harris RA, Jeong D, Lee IK. α-Lipoic acid attenuates vascular calcification via reversal of mitochondrial function and restoration of Gas6/Axl/Akt survival pathway. J Cell Mol Med. 2012; 16:273–286. DOI: 10.1111/j.1582-4934.2011.01294.x [PubMed: 21362131]

Klass MR. A method for the isolation of longevity mutants in the nematode Caenorhabditis elegans and initial results. Mech Ageing Dev. 1983; 22:279–286. [PubMed: 6632998]

Koob M, Laugel V, Durand M, Fothergill H, Dalloz C, Sauvanaud F, Dollfus H, Namer IJ, Dietemann JL. Neuroimaging In Cockayne Syndrome. Am J Neuroradiol. 2010; 31:1623–1630. DOI: 10.3174/ajnr.A2135 [PubMed: 20522568]

Kraemer KH, Patronas NJ, Schiffmann R, Brooks BP, Tamura D, DiGiovanna JJ. XERODERMA PIGMENTOSUM, TRICHOTHIODYSTROPHY AND COCKAYNE SYNDROME: A COMPLEX GENOTYPE-PHENOTYPE RELATIONSHIP. Neuroscience. 2007; 145:1388–1396. DOI: 10.1016/j.neuroscience.2006.12.020 [PubMed: 17276014]

Kristensen U, Epanchintsev A, Rauschendorf MA, Laugel V, Stevnsner T, Bohr VA, Coin F, Egly JM. Regulatory interplay of Cockayne syndrome B ATPase and stress-response gene ATF3 following genotoxic stress. Proc Natl Acad Sci. 2013; 110:E2261–E2270. DOI: 10.1073/pnas.1220071110 [PubMed: 23733932]

Krols M, van Isterdael G, Asselbergh B, Kremer A, Lippens S, Timmerman V, Janssens S. Mitochondria-associated membranes as hubs for neurodegeneration. Acta Neuropathol (Berl). 2016; 131:505–523. DOI: 10.1007/s00401-015-1528-7 [PubMed: 26744348]

Kubota M, Ohta S, Ando A, Koyama A, Terashima H, Kashii H, Hoshino H, Sugita K, Hayashi M. Nationwide survey of Cockayne syndrome in Japan: Incidence, clinical course and prognosis. Pediatr Int. 2015; 57:339–347. DOI: 10.1111/ped.12635 [PubMed: 25851792]

Lahiri S, Davies N. Cockayne's Syndrome: case report of a successful pregnancy. BJOG Int J Obstet Gynaecol. 2003; 110:871–872.

Lai CH, Chou CY, Ch'ang LY, Liu CS, Lin W. Identification of novel human genes evolutionarily conserved in Caenorhabditis elegans by comparative proteomics. Genome Res. 2000; 10:703–713. [PubMed: 10810093]

Lans H, Marteijn JA, Schumacher B, Hoeijmakers JHJ, Jansen G, Vermeulen W. Involvement of global genome repair, transcription coupled repair, and chromatin remodeling in UV DNA damage response changes during development. PLoS Genet. 2010; 6:e1000941.doi: 10.1371/journal.pgen.1000941 [PubMed: 20463888]

Laposa RR, Huang EJ, Cleaver JE. Increased apoptosis, p53 up-regulation, and cerebellar neuronal degeneration in repair-deficient Cockayne syndrome mice. Proc Natl Acad Sci U S A. 2007; 104:1389–1394. DOI: 10.1073/pnas.0610619104 [PubMed: 17229834]

Lascaratos G, Chau KY, Zhu H, Gkotsi D, King R, Gout I, Kamal D, Luthert PJ, Schapira AHV, Garway-Heath DF. Resistance to the most common optic neuropathy is associated with systemic mitochondrial efficiency. Neurobiol Dis. 2015; 82:78–85. DOI: 10.1016/j.nbd.2015.05.012 [PubMed: 26054436]

Laugel V. Cockayne syndrome: The expanding clinical and mutational spectrum. Mech Ageing Dev, Special Issue on the segmental progeria Cockayne syndrome. 2013; 134:161–170. DOI: 10.1016/j.mad.2013.02.006

Laugel V. Cockayne Syndrome. GeneReviews(®). 1993

Le Belle JE, Orozco NM, Paucar AA, Saxe JP, Mottahedeh J, Pyle AD, Wu H, Kornblum HI. Proliferative neural stem cells have high endogenous ROS levels that regulate self-renewal and neurogenesis in a PI3K/Akt-dependant manner. Cell Stem Cell. 2011; 8:59–71. DOI: 10.1016/j.stem.2010.11.028 [PubMed: 21211782]

Lee MH, Ahn B, Choi IS, Koo HS. The gene expression and deficiency phenotypes of Cockayne syndrome B protein in Caenorhabditis elegans. FEBS Lett. 2002; 522:47–51. [PubMed: 12095617]

Lee SJ, Jeong JY, Oh CJ, Park S, Kim JY, Kim HJ, Doo Kim N, Choi YK, Do JY, Go Y, Ha CM, Choi JY, Huh S, Ho Jeoung N, Lee KU, Choi HS, Wang Y, Park KG, Harris RA, Lee IK. Pyruvate Dehydrogenase Kinase 4 Promotes Vascular Calcification via SMAD1/5/8 Phosphorylation. Sci Rep. 2015; 5doi: 10.1038/srep16577

Leech RW, Brumback RA, Miller RH, Otsuka F, Tarone RE, Robbins JH. Cockayne Syndrome: Clinicopathologic and Tissue Culture Studies of Affected Siblings. J Neuropathol Exp Neurol. 1985; 44:507–519. DOI: 10.1097/00005072-198509000-00006 [PubMed: 4031953]

Lehmann AR. DNA repair-deficient diseases, xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. Biochimie, DNA repair pathways and associated human diseases. 2003; 85:1101–1111. DOI: 10.1016/j.biochi.2003.09.010

Lehmann AR, Kirk-Bell S, Mayne L. Abnormal Kinetics of DNA Synthesis in Ultraviolet Light-irradiated Cells from Patients with Cockayne's Syndrome. Cancer Res. 1979; 39:4237–4241. [PubMed: 157803]

Lindenbaum Y, Dickson D, Rosenbaum P, Kraemer K, Robbins I, Rapin I. Xeroderma pigmentosum/cockayne syndrome complex: first neuropathological study and review of eight other cases. Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc. 2001; 5:225–242. DOI: 10.1053/ejpn.2001.0523

Livingston JH, Stivaros S, van der Knaap MS, Crow YJ. Recognizable phenotypes associated with intracranial calcification. Dev Med Child Neurol. 2013; 55:46–57. DOI: 10.1111/j.1469-8749.2012.04437.x [PubMed: 23121296]

Livingston JH, Stivaros S, Warren D, Crow YJ. Intracranial calcification in childhood: a review of aetiologies and recognizable phenotypes. Dev Med Child Neurol. 2014; 56:612–626. DOI: 10.1111/dmcn.12359 [PubMed: 24372060]

Love DC, Ghosh S, Mondoux MA, Fukushige T, Wang P, Wilson MA, Iser WB, Wolkow CA, Krause MW, Hanover JA. Dynamic O-GlcNAc cycling at promoters of Caenorhabditis elegans genes regulating longevity, stress, and immunity. Proc Natl Acad Sci U S A. 2010; 107:7413–7418. DOI: 10.1073/pnas.0911857107 [PubMed: 20368426]

Lowry RB, MacLean R, McLean DM, Tischler B. Cataracts, microcephaly, kyphosis, and limited joint movement in two siblings: a new syndrome. J Pediatr. 1971; 79:282–284. [PubMed: 5560051]

Mao H, Seo SJ, Biswal MR, Li H, Conners M, Nandyala A, Jones K, Le YZ, Lewin AS. Mitochondrial oxidative stress in the retinal pigment epithelium leads to localized retinal degeneration. Invest Ophthalmol Vis Sci. 2014; 55:4613–4627. DOI: 10.1167/iovs.14-14633 [PubMed: 24985474]

Marteijn JA, Lans H, Vermeulen W, Hoeijmakers JHJ. Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol. 2014; 15:465–481. DOI: 10.1038/nrm3822 [PubMed: 24954209]

Mayne LV, Lehmann AR. Failure of RNA Synthesis to Recover after UV Irradiation: An Early Defect in Cells from Individuals with Cockayne's Syndrome and Xeroderma Pigmentosum. Cancer Res. 1982; 42:1473–1478. [PubMed: 6174225]

McElvanney AM, Wooldridge WJ, Khan AA, Ansons AM. Ophthalmic management of Cockayne's syndrome. Eye Lond Engl. 1996; 10(Pt 1):61–64. DOI: 10.1038/eye.1996.9

McKinnon PJ. DNA repair deficiency and neurological disease. Nat Rev Neurosci. 2009; 10:100–112. DOI: 10.1038/nrn2559 [PubMed: 19145234]

Meyer JN, Boyd WA, Azzam GA, Haugen AC, Freedman JH, Van Houten B. Decline of nucleotide excision repair capacity in aging Caenorhabditis elegans. Genome Biol. 2007; 8:R70.doi: 10.1186/gb-2007-8-5-r70 [PubMed: 17472752]

Mintun MA, Lundstrom BN, Snyder AZ, Vlassenko AG, Shulman GL, Raichle ME. Blood flow and oxygen delivery to human brain during functional activity: Theoretical modeling and experimental data. Proc Natl Acad Sci. 2001; 98:6859–6864. DOI: 10.1073/pnas.111164398 [PubMed: 11381119]

Mizuguchi M, Itoh M. A 35-year-old female with growth and developmental retardation, progressive ataxia, dementia and visual loss. Neuropathology. 2005; 25:103–106. DOI: 10.1111/j.1440-1789.2004.00589.x [PubMed: 15822826]

Mizuno Y, Takahashi K, Igarashi T, Saito M, Mizuguchi M. Congenital infection-like syndrome with intracranial calcification. Brain Dev. 2011; 33:530–533. DOI: 10.1016/j.braindev.2010.09.001 [PubMed: 20926212]

Motojima T, Sugita K, Omata T, Fujii K. Clinical examination of renal function in Cockayne syndrome. No Hattatsu Brain Dev. 2014; 46:311–314.

Murakami S, Johnson TE. A genetic pathway conferring life extension and resistance to UV stress in Caenorhabditis elegans. Genetics. 1996; 143:1207–1218. [PubMed: 8807294]

Nagtegaal AP, Rainey RN, van der Pluijm I, Brandt RMC, van der Horst GTJ, Borst JGG, Segil N. Cockayne Syndrome Group B (Csb) and Group A (Csa) Deficiencies Predispose to Hearing Loss and Cochlear Hair Cell Degeneration in Mice. J Neurosci. 2015; 35:4280–4286. DOI: 10.1523/JNEUROSCI.5063-14.2015 [PubMed: 25762674]

Nance MA, Berry SA. Cockayne syndrome: Review of 140 cases. Am J Med Genet. 1992; 42:68–84. DOI: 10.1002/ajmg.1320420115 [PubMed: 1308368]

Natale V. A comprehensive description of the severity groups in Cockayne syndrome. Am J Med Genet A. 2011; 155:1081–1095. DOI: 10.1002/ajmg.a.33933

Neilan EG, Delgado MR, Donovan MA, et al. REsponse of motor complications in cockayne syndrome to carbidopalevodopa. Arch Neurol. 2008; 65:1117–1121. DOI: 10.1001/archneur.65.8.1117 [PubMed: 18695064]

Neill CA, Dingwall MM. A syndrome resembling progeria: A review of two cases. Arch Dis Child. 1950; 25:213–223. [PubMed: 14783428]

Osenbroch PØ, Auk-Emblem P, Halsne R, Strand J, Forstrøm RJ, van der Pluijm I, Eide L. Accumulation of mitochondrial DNA damage and bioenergetic dysfunction in CSB defective cells. FEBS J. 2009; 276:2811–2821. DOI: 10.1111/j.1742-4658.2009.07004.x [PubMed: 19389114]

Ovaert C, Cano A, Chabrol B. Aortic dilatation in Cockayne syndrome. Am J Med Genet A. 2007; 143A:2604–2606. DOI: 10.1002/ajmg.a.31986 [PubMed: 17935247]

Pascucci B, Lemma T, Iorio E, Giovannini S, Vaz B, Iavarone I, Calcagnile A, Narciso L, Degan P, Podo F, Roginskya V, Janjic BM, Van Houten B, Stefanini M, Dogliotti E, D'Errico M. An altered redox balance mediates the hypersensitivity of Cockayne syndrome primary fibroblasts to oxidative stress. Aging Cell. 2012; 11:520–529. DOI: 10.1111/j.1474-9726.2012.00815.x [PubMed: 22404840]

Pasquier L, Laugel V, Lazaro L, Dollfus H, Journel H, Edery P, Goldenberg A, Martin D, Heron D, Le Merrer M, Rustin P, Odent S, Munnich A, Sarasin A, Cormier-Daire V. Wide clinical variability among 13 new Cockayne syndrome cases confirmed by biochemical assays. Arch Dis Child. 2006; 91:178–182. DOI: 10.1136/adc.2005.080473 [PubMed: 16428367]

Piana RL, Uggetti C, Roncarolo F, Vanderver A, Olivieri I, Tonduti D, Helman G, Balottin U, Fazzi E, Crow YJ, Livingston J, Orcesi S. Neuroradiologic patterns and novel imaging findings in Aicardi-Goutières syndrome. Neurology. 2016; 86:28–35. DOI: 10.1212/WNL.0000000000002228 [PubMed: 26581299]

Ramantani G, Niggemann P, Bast T, Lee-Kirsch MA. Reconciling Neuroimaging and Clinical Findings in Aicardi-Goutières Syndrome: An Autoimmune-Mediated Encephalopathy. Am J Neuroradiol. 2010; 31:E62–E63. DOI: 10.3174/ajnr.A2147 [PubMed: 20581073]

Rangaraju S, Solis GM, Thompson RC, Gomez-Amaro RL, Kurian L, Encalada SE, Niculescu AB, Salomon DR, Petrascheck M. Suppression of transcriptional drift extends C. elegans lifespan by postponing the onset of mortality. eLife. 2015; 4:e08833.doi: 10.7554/eLife.08833 [PubMed: 26623667]

Rapin I. Chapter 167 - Disorders of nucleotide excision repair. Handb Clin Neurol, Pediatric Neurology Part III. 2013; 113:1637–1650.

Rapin I, Lindenbaum Y, Dickson DW, Kraemer KH, Robbins JH. Cockayne syndrome and xeroderma pigmentosum DNA repair disorders with overlaps and paradoxes. Neurology. 2000; 55:1442–1449. DOI: 10.1212/WNL.55.10.1442 [PubMed: 11185579]

Rapin I, Weidenheim K, Lindenbaum Y, Rosenbaum P, Merchant SN, Krishna S, Dickson DW. Cockayne Syndrome in Adults: Review With Clinical and Pathologic Study of a New Case. J Child Neurol. 2006; 21:991–1006. [PubMed: 17092472]

Reiss U, Hofweber K, Herterich R, Waldherr R, Bohnert E, Jung E, Schärer K. Nephrotic syndrome, hypertension, and adrenal failure in atypical Cockayne syndrome. Pediatr Nephrol Berl Ger. 1996; 10:602–605.

Sato H, Saito T, Kurosawa K, Ootaka T, Furuyama T, Yoshinaga K. Renal lesions in Cockayne's syndrome. Clin Nephrol. 1988; 29:206–209. [PubMed: 3365865]

Scaioli V, D'Arrigo S, Pantaleoni C. Unusual neurophysiological features in Cockayne's syndrome: a report of two cases as a contribution to diagnosis and classification. Brain Dev. 2004; 26:273–280. DOI: 10.1016/S0387-7604(03)00130-X [PubMed: 15130695]

Scheibye-Knudsen M, Fang EF, Croteau DL, Bohr VA. Contribution of defective mitophagy to the neurodegeneration in DNA repair-deficient disorders. Autophagy. 2014a; 10:1468–1469. DOI: 10.4161/auto.29321 [PubMed: 24991831]

Scheibye-Knudsen M, Fang EF, Croteau DL, Wilson DM III, Bohr VA. Protecting the mitochondrial powerhouse. Trends Cell Biol. 2015; 25:158–170. DOI: 10.1016/j.tcb.2014.11.002 [PubMed: 25499735]

Scheibye-Knudsen M, Mitchell SJ, Fang EF, Iyama T, Ward T, Wang J, Dunn CA, Singh N, Veith S, Hasan-Olive MM, Mangerich A, Wilson MA, Mattson MP, Bergersen LH, Cogger VC, Warren A, Le Couteur DG, Moaddel R, Wilson DM III, Croteau DL, de Cabo R, Bohr VA. A High-Fat Diet and NAD+ Activate Sirt1 to Rescue Premature Aging in Cockayne Syndrome. Cell Metab. 2014b; 20:840–855. DOI: 10.1016/j.cmet.2014.10.005 [PubMed: 25440059]

Scheibye-Knudsen M, Ramamoorthy M, Sykora P, Maynard S, Lin PC, Minor RK, Wilson DM III, Cooper M, Spencer R, de Cabo R, Croteau DL, Bohr VA. Cockayne syndrome group B protein prevents the accumulation of damaged mitochondria by promoting mitochondrial autophagy. J Exp Med. 2012; 209:855–869. DOI: 10.1084/jem.20111721 [PubMed: 22473955]

Scheibye-Knudsen M, Scheibye-Alsing K, Canugovi C, Croteau DL, Bohr VA. A novel diagnostic tool reveals mitochondrial pathology in human diseases and aging. Aging. 2013; 5:192–208. [PubMed: 23524341]

Schenone A, Rolando S, Ferrari M, Romagnoli P, Tabaton M, Mancardi GL. Peripheral neuropathy in Cockayne syndrome. Ital J Neurol Sci. 1986; 7:447–452. [PubMed: 3019920]

Selekler K. Calcification of the basal ganglia on computed tomography. Schweiz Arch Für Neurol Neurochir Psychiatr Arch Suisses Neurol Neurochir Psychiatr. 1982; 131:187–195.

Shemen LJ, Mitchell DP, Farkashidy J. Cockayne syndrome–an audiologic and temporal bone analysis. Am J Otol. 1984; 5:300–307. [PubMed: 6720882]

Soffer D, Grotsky HW, Rapin I, Suzuki K. Cockayne syndrome: unusual neuropathological findings and review of the literature. Ann Neurol. 1979; 6:340–348. DOI: 10.1002/ana.410060407 [PubMed: 400082]

Someya S, Prolla TA. Mitochondrial oxidative damage and apoptosis in age-related hearing loss. Mech Ageing Dev. 2010; 131:480–486. DOI: 10.1016/j.mad.2010.04.006 [PubMed: 20434479]

Stefanini M, Fawcett H, Botta E, Nardo T, Lehmann AR. Genetic analysis of twenty-two patients with Cockayne syndrome. Hum Genet. 1996; 97:418–423. [PubMed: 8834235]

Stevnsner T, Muftuoglu M, Aamann MD, Bohr VA. The role of Cockayne Syndrome group B (CSB) protein in base excision repair and aging. Mech Ageing Dev. 2008; 129:441–448. DOI: 10.1016/j.mad.2008.04.009 [PubMed: 18541289]

Stevnsner T, Nyaga S, de Souza-Pinto NC, van der Horst GTJ, Gorgels TGMF, Hogue BA, Thorslund T, Bohr VA. Mitochondrial repair of 8-oxoguanine is deficient in Cockayne syndrome group B. Oncogene. 2002; 21:8675–8682. DOI: 10.1038/sj.onc.1205994 [PubMed: 12483520]

Stroustrup N, Anthony WE, Nash ZM, Gowda V, Gomez A, López-Moyado IF, Apfeld J, Fontana W. The temporal scaling of Caenorhabditis elegans ageing. Nature. 2016; 530:103–107. DOI: 10.1038/nature16550 [PubMed: 26814965]

Su B, Ji YS, Sun X, Liu XH, Chen ZY. Brain-derived Neurotrophic Factor (BDNF)-induced Mitochondrial Motility Arrest and Presynaptic Docking Contribute to BDNF-enhanced Synaptic Transmission. J Biol Chem. 2014; 289:1213–1226. DOI: 10.1074/jbc.M113.526129 [PubMed: 24302729]

Sugarman GI, Landing BH, Reed WB. Cockayne syndrome: clinical study of two patients and neuropathologic findings in one. Clin Pediatr (Phila). 1977; 16:225–232. [PubMed: 837626]

Traboulsi EI, De Becker I, Maumenee IH. Ocular findings in Cockayne syndrome. Am J Ophthalmol. 1992a; 114:579–583. [PubMed: 1443019]

Traboulsi EI, De Becker I, Maumenee IH. Ocular findings in Cockayne syndrome. Am J Ophthalmol. 1992b; 114:579–583. [PubMed: 1443019]

Troelstra C, van Gool A, de Wit J, Vermeulen W, Bootsma D, Hoeijmakers JH. ERCC6, a member of a subfamily of putative helicases, is involved in Cockayne's syndrome and preferential repair of active genes. Cell. 1992; 71:939–953. [PubMed: 1339317]

van der Horst GT, van Steeg H, Berg RJ, van Gool AJ, de Wit J, Weeda G, Morreau H, Beems RB, van Kreijl CF, de Gruijl FR, Bootsma D, Hoeijmakers JH. Defective transcription-coupled repair in Cockayne syndrome B mice is associated with skin cancer predisposition. Cell. 1997; 89:425–435. [PubMed: 9150142]

van der Horst GTJ, Meira L, Gorgels TGMF, de Wit J, Velasco-Miguel S, Richardson JA, Kamp Y, Vreeswijk MPG, Smit B, Bootsma D, Hoeijmakers JHJ, Friedberg EC. UVB radiation-induced cancer predisposition in Cockayne syndrome group A (Csa) mutant mice. DNA Repair. 2002; 1:143–157. [PubMed: 12509261]

Villa-Bellosta R, Rivera-Torres J, Osorio FG, Acín-Pérez R, Enriquez JA, López-Otín C, Andrés V. Defective extracellular pyrophosphate metabolism promotes vascular calcification in a mouse model of Hutchinson-Gilford progeria syndrome that is ameliorated on pyrophosphate treatment. Circulation. 2013; 127:2442–2451. DOI: 10.1161/CIRCULATIONAHA.112.000571 [PubMed: 23690466]

Vos A, Gabreëls-Festen A, Joosten E, Gabreëls F, Renier W, Mullaart R. The neuropathy of Cockayne syndrome. Acta Neuropathol (Berl). 1983; 61:153–156. [PubMed: 6314729]

Wagner MW, Poretti A, Wang T, Crawford TO, Huisman TAGM, Bosemani T. Susceptibility-Weighted Imaging for Calcification in Cockayne Syndrome. J Pediatr. 2014; 165:416–416.e1. DOI: 10.1016/j.jpeds.2014.04.030 [PubMed: 24857520]

Wang Y, Jones-Tabah J, Chakravarty P, Stewart A, Muotri A, Laposa RR, Svejstrup JQ. Pharmacological Bypass of Cockayne Syndrome B Function in Neuronal Differentiation. Cell Rep. 2016; 14:2554–2561. DOI: 10.1016/j.celrep.2016.02.051 [PubMed: 26972010]

Wei L, Nakajima S, Böhm S, Bernstein KA, Shen Z, Tsang M, Levine AS, Lan L. DNA damage during the G0/G1 phase triggers RNA-templated, Cockayne syndrome B-dependent homologous recombination. Proc Natl Acad Sci U S A. 2015; 112:E3495–3504. DOI: 10.1073/pnas.1507105112 [PubMed: 26100862]

Weidenheim KM, Dickson DW, Rapin I. Neuropathology of Cockayne syndrome: Evidence for impaired development, premature aging, and neurodegeneration. Mech Ageing Dev. 2009; 130:619–636. DOI: 10.1016/j.mad.2009.07.006 [PubMed: 19647012]

Wilson BT, Stark Z, Sutton RE, Danda S, Ekbote AV, Elsayed SM, Gibson L, Goodship JA, Jackson AP, Keng WT, King MD, McCann E, Motojima T, Murray JE, Omata T, Pilz D, Pope K, Sugita K, White SM, Wilson IJ. The Cockayne Syndrome Natural History (CoSyNH) study: clinical findings in 102 individuals and recommendations for care. Genet Med. 2015; doi: 10.1038/gim.2015.110

Wilson NM, Hilmer SN, March LM, Cameron ID, Lord SR, Seibel MJ, Sambrook PN. Associations between drug burden index and physical function in older people in residential aged care facilities. Age Ageing. 2010; 39:503–507. DOI: 10.1093/ageing/afq053 [PubMed: 20501606]

Yu E, Calvert PA, Mercer JR, Harrison J, Baker L, Figg NL, Kumar S, Wang JC, Hurst LA, Obaid DR, Logan A, West NEJ, Clarke MCH, Vidal-Puig A, Murphy MP, Bennett MR. Mitochondrial DNA Damage Can Promote Atherosclerosis Independently of Reactive Oxygen Species Through Effects on Smooth Muscle Cells and Monocytes and Correlates With Higher-Risk Plaques in Humans. Circulation. 2013; 128:702–712. DOI: 10.1161/CIRCULATIONAHA.113.002271 [PubMed: 23841983]

Yuen MK, Chandra Rodrigo MR, Law Min JC, Antonio Tong CK. Myocardial ischemia and delayed recovery after anesthesia in a patient with Cockayne syndrome: A case report. J Oral Maxillofac Surg. 2001; 59:1488–1491. DOI: 10.1053/joms.2001.28291 [PubMed: 11732042]

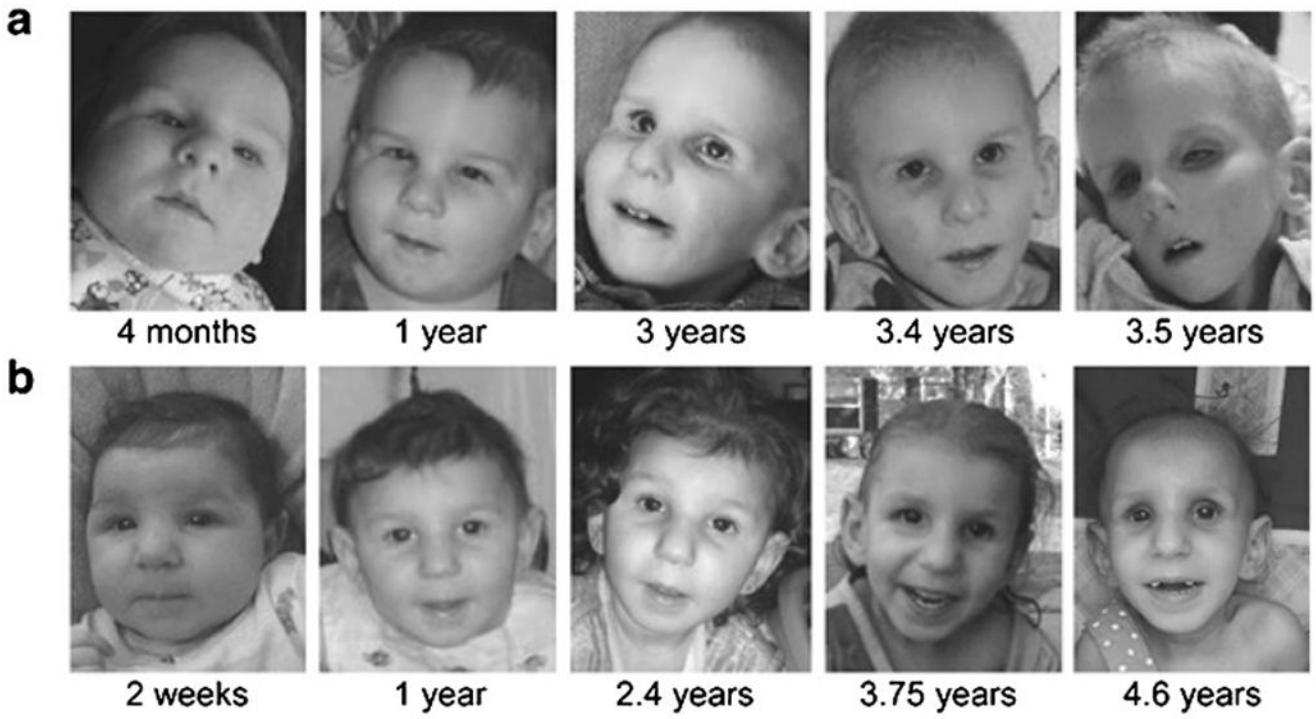

Figure 1.

Shows the progressive loss of facial subcutaneous fat over time, leading to sunken eyes and the ‘wizened’ facies typical of CS patients (reproduced with permission from (Wilson et al., 2015, fig. 2a, 2b).

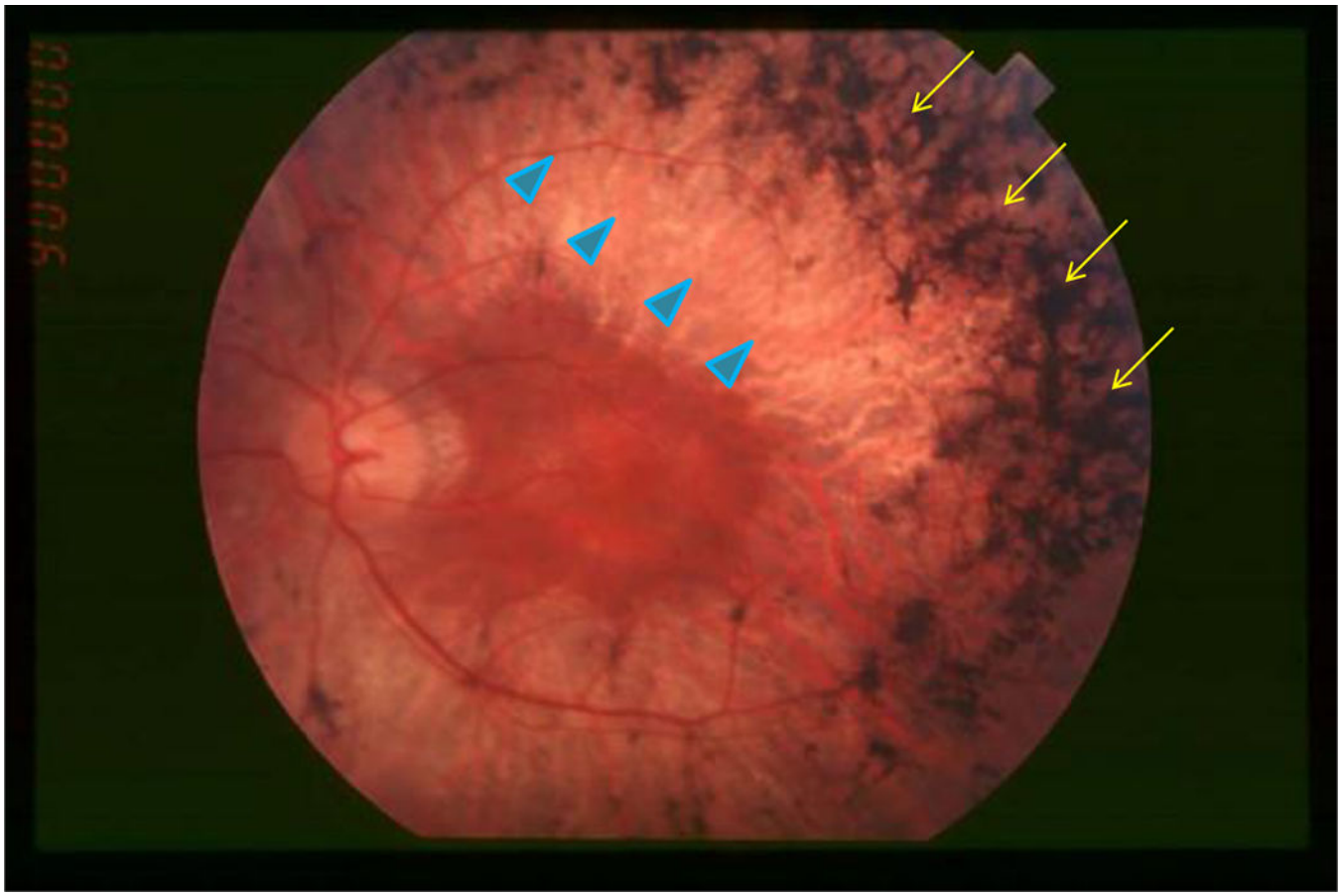

Figure 2.

Fundoscopic examination of the retina shows the typical retinal pigmentary “leak” in a salt and pepper pattern. The yellow arrows indicate the areas of involvement, while the blue arrows indicate areas of relatively preserved retina (reproduced with permission from Orphanet Journal of Rare Diseases) (Hamel, 2006, fig. 1).

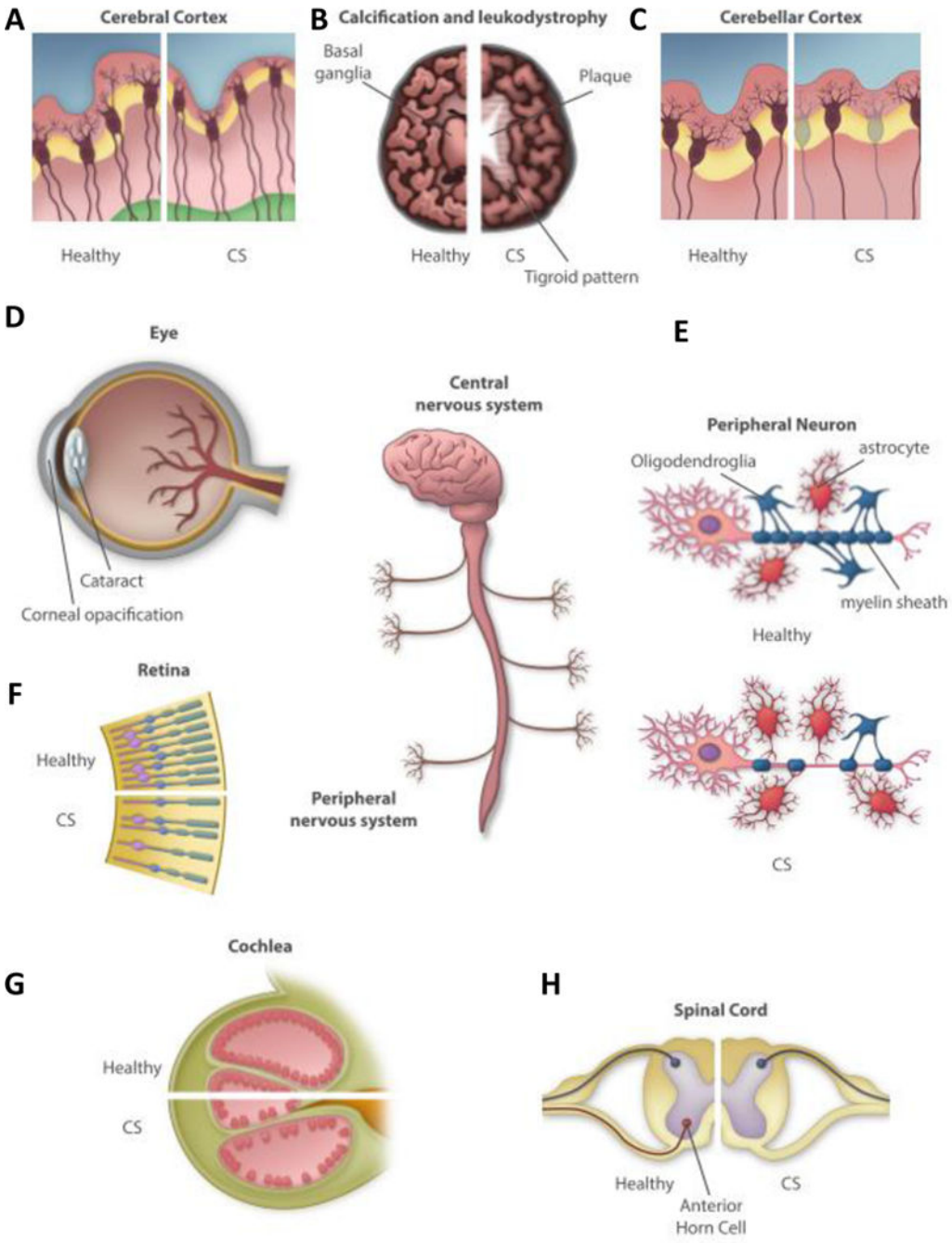

Figure 3.

Some of the most important clinical manifestations of CS are shown. Figure 3A: Cerebral cortex - may be slightly thinned, with relative preservation of cortical neurons. Figure 3B: White matter changes - There is “tigroid leukodystrophy”, with areas that have relatively less leukodystrophy interspersed with more affected areas in a pattern resembling the stripes on a tiger. Figure 3C: Cerebellum - There is loss of Purkinje cells. Figure 3D: Eye - Cataracts and corneal opacification are seen in CS patients. Figure 3E: Neurons – There are fewer oligodendroglia, and less myelin is produced, leading to a demyelinating neuropathy.

Increased numbers of astrocytes are seen in areas of myelin and oligodendroglia loss. It has not been clearly established whether the astrocytes are the cause of or (more possibly) reactive to the changes in myelin and oligodendroglia. Figure 3F: Retina – shows loss of rods and cones, the photoreceptor cells, and also of ganglion and outer nuclear cell layers. Figure 3G: Cochlea – shows loss of hair cells. This is most pronounced generally in the basal turn of the cochlea. Figure 3H: Spinal cord – may show loss of anterior horn cells. It is not clear whether this is the primary event or secondary (and retrograde) to neuronal loss.

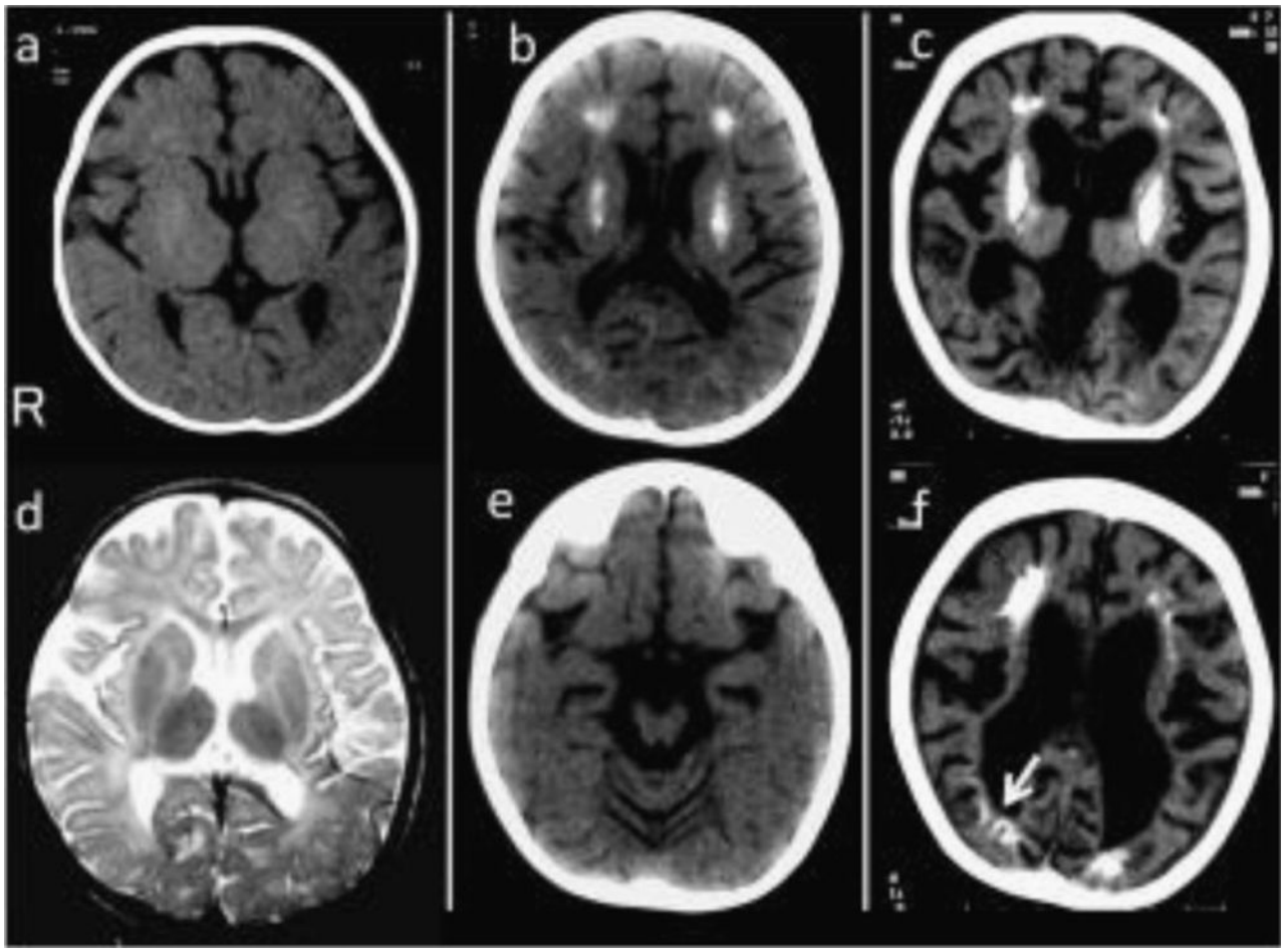

Figure 4.

The brain calcifications in CS are a pathognomonic feature. They are mainly in the deep white matter, especially the basal ganglia, and progress with age. Some calcification can also occur in the depths of the sulci (white arrow in figure f). Also note the progressive brain atrophy (reproduced with permission from Kubota et al) (Kubota et al., 2015, fig. 4).

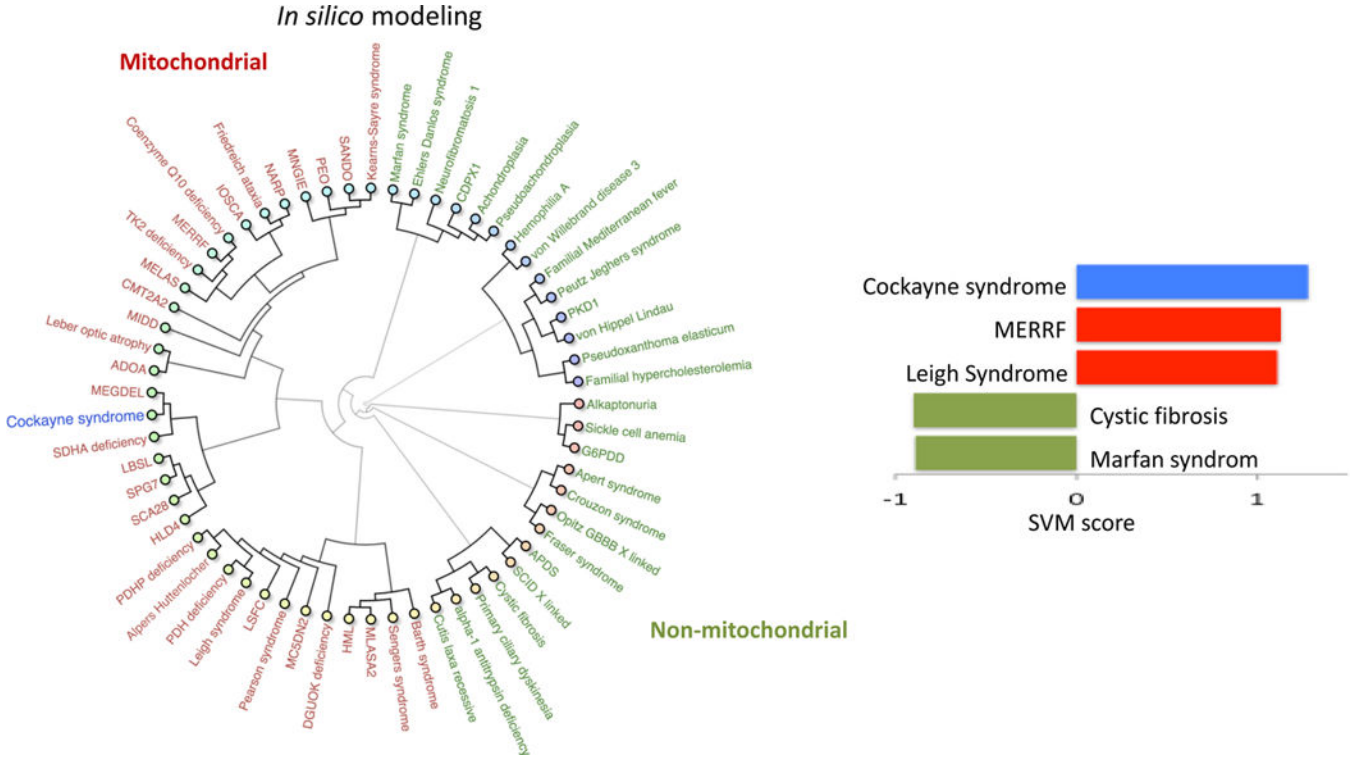

Figure 5.

Molecule to medicine. *In silico* analyses show association of Cockayne syndrome with mitochondrial diseases using methods such as hierarchical clustering and a support vector machine.

Table 1

Summary of clinical features of CS

	Clinical features	Pathology
Facies	Wizened facies. Sunken eyes, large ears, thin pointy nose. Small chin. Dental caries, enamel hypoplasia (Laugel, 2013)	
Skin, hair, nails	Photosensitivity. Wrinkled and aged appearing skin. Thin dry hair, prematurely gray hair (Leech et al., 1985; Sugarman et al., 1977; Weidenheim et al., 2009). Poor venous access.	
Central nervous system	Microcephaly usually beginning at age 2(Nance and Berry, 1992; Weidenheim et al., 2009). Mental retardation with low IQ. Delayed milestones(Wilson et al., 2015). Tremors, ataxia, seizures (Rapin et al., 2006). Strokes and subdural hemorrhages(Koob et al., 2010; Rapin et al., 2006; Weidenheim et al., 2009)	Demyelination – is patchy and segmental– "tigroid leukodystrophy (Koob et al., 2010; Rapin et al., 2006)." Both oligodendroglia and Schwann cells are affected. Affects cerebral white matter, corpus callosum, brainstem, spinal cord and peripheral nerves. Neuronal loss at multiple sites, especially cerebellum. Loss of anterior horns cells due to anterograde and/or retrograde degeneration (Weidenheim et al., 2009). Calcification [55–95%] of the cerebral cortex (especially depths of sulci (Koob et al., 2010)), basal ganglia, cerebellum, thalamus; also of the arteries, arterioles and capillaries. Vascular changes - String vessels, especially in areas of tigroid leukodystrophy (Rapin et al., 2006), calcification in leptomeningeal vessels, accelerated atherosclerosis and arteriolosclerosis (Hayashi et al., 2012, 2001; Itoh et al., 1999; Mizuguchi and Itoh, 2005). Gliosis is present. Astrocytes and microglia may show irregular cytoplasm, multiple nuclei. May be seen as high intensity white matter on FLAIR MRI sequences signals (Koob et al., 2010). No major brain malformations. Relative sparing of cerebral cortex, slight thinning of cortical ribbon may be seen. Normal gyral pattern with widening of sulci. Lamination, neuronal size and configuration of neocortex are preserved. May show parieto-occipital dominance. Severe cerebellar atrophy. Loss of Purkinje, granular neurons, and in some cases neurons in the dentate nucleus. Dendrites of Purkinje cells may be grossly deformed ("cactus flowers"), ferruginated dendrites. Dendrites have fewer higher order branches. Purkinje "axonal torpedoes" may be present (Koob et al., 2010; Weidenheim et al., 2009). Ventricular enlargement, enlarged cisterna magna are seen. Amyloid plaques, neurofibrillary tangles, Hirano bodies not commonly seen, although ubiquitin reactivity of axons present (Itoh et al., 1999).
Hearing and vestibular systems	Sensorineural, high tone hearing loss [60–90%]. Mixed conductive and sensorinueral hearing loss (44%)(Wilson et al., 2015). Most commonly bilateral, rarely unilateral (Wilson et al., 2015).	Loss of hair cells in cochlea, particularly in the basal turn. Loss of neurons in spiral ganglion. Atrophy of auditory pathways (Gandolfi et al., 1984; Rapin et al., 2006; Shemen et al., 1984). Scala communis, thickened stapes crurae, widened prototympanum(Rapin et al., 2006). Loss of hair cells in pars superior. Loss of neurons in vestibular ganglion. Collapse of the endolymphatic duct of pars inferior (Rapin et al., 2006).
Vision	Corneal opacification. Cataracts [36–86%]. Usually bilateral, most develop by 4 years of age. Pigmentary retinopathy ("salt and pepper")[43–89%] (Kubota et al., 2015; Nance and Berry, 1992; Wilson et al., 2015). Miotic pupils(Dollfus et al., 2003; Traboulsi et al., 1992b). Optic disk pallor. Enophthalmos. Narrow palpebral fissures.	Patchy loss of melanin pigment granules. Lipofuscin deposition, large pigment laden cells in a perivascular distribution. Retinal pigment epithelial atrophy and hyperplasia. Loss of cells in ganglion and outer nuclear cell layers (Rapin et al., 2006). Both outer and inner segments of photoreceptors are affected. Optic nerve atrophy, with partial demyelination, axonal loss, and gliosis (Nance and Berry, 1992).
Musculoskeletal system	Cachectic dwarfism. Contractures. Kyphosis, scoliosis. Stooped posture. Muscle wasting.	Denervation myopathy, disuse atrophy
Cardiovascular system	Accelerated hypertension.	Increased intima medial thickening (Crome and Kanjilal, 1971; Higginbottom et al., 1979). Atherosclerosis, arteriosclerosis.

	Clinical features	Pathology
	Aortic root dilatation(Ovaert et al., 2007). Cardiomyopathy(Choong et al., 1997; Yuen et al., 2001)	
Gastrointestinal system	Severe reflux. Abnormal gastrointestinal motility. Many have percutaneous gastrostomy tubes. Hepatomegaly, splenomegaly, elevated liver enzymes. Altered metabolism of drugs(Wilson et al., 2015).	
Renal system	Renal failure	Renal arteries show changes of advanced atherosclerosis and arteriolosclerosis. Unilateral or hypoplastic kidneys (Funaki et al., 2006; Higginbottom et al., 1979; Hirooka et al., 1988; Motojima et al., 2014; Reiss et al., 1996; Sato et al., 1988).
Reproductive systems		
Males	Micropenis, smaller testicular size (Inoue et al., 1997)	
Females	Ovarian atrophy. Successful pregnancy has been reported (Lahiri and Davies, 2003).	
Endocrine systems	Normal secondary sexual characteristics(Weidenheim et al., 2009). Normal growth hormone, thyroid stimulating hormone, calcium levels (Inoue et al., 1997; Sugarman et al., 1977)	Normal pituitary gland and thyroid gland
Eccrine systems	Decreased production of sweat, tears, saliva	

Table 2

Comparison of clinical features from different reviews of CS

Clinical feature	Article	Age	Modifiers	Relationship to disease process
Hearing loss	Wilson	84% by 10 years	Almost exclusively bilateral. Mixed type	
	Kubota	After 2–3 years of age. Observed in > 90% of cases.	By age 2 in CS2, improved with hearing aid. 60–70 db hearing loss.	
	Nance and Berry	May not be manifest till teenage years. 60 percent affected.	Sensorineural. Bilateral, mild to severe.	
	Rapin	–	High tone hearing loss. Progressive, almost every case in the series.	
	Natale	May be universal, but not occur until a patient's condition starts to decline. Occurs in >2/3rds of patients.	Progressive. Affects quality of life. Often occurred suddenly or over 2–3 days.	
Cataracts	Wilson	86% by 4 years. 48.5% overall had cataracts. Approximately 90% were bilateral. Prevalence increases till approximately 4 years of age, and then plateaus.	Most cases are B/L	A cataract before 3 years of age is the most valuable prognostic factor. Also associated with time to development of hearing loss and contractures, but not tremor.
	Kubota	64.5 percent of patients		
	Nance and Berry	36 percent of patients.		Presence of cataracts less than 3 years of age are predictors of severe disease and early death.
	Rapin		Type 2 is associated with congenital cataracts.	
	Natale	1/3 to 2/3 of patients.	Cataracts occurred across all severity groups.	Congenital cataracts do not correlate with poor prognosis.
Retinal dystrophy	Wilson	43%		
	Kubota	89.3%		
	Nance and Berry	55%	Progressive retinal degeneration is the most common eye disturbance.	
	Rapin	68%		
	Natale	1/3–2/3 of patients		
Basal ganglia calcification	Wilson	55%	Principally affects basal ganglia. Iron present.	Not pathognomonic or prognostic or clinically actionable.
	Kubota	>96.6%. After 2–3 years of age.	Bilateral calcification of the basal ganglia is a diagnostic hallmark of CS. May not occur before the age of 1 even in CS2.	No correlation with age, severity of neurological symptoms or degree of cerebral atrophy.
	Nance and Berry		Most found in a perivascular distribution in the basal ganglia and dentate nucleus.	

Clinical feature	Article	Age	Modifiers	Relationship to disease process
	Rapin		Calcification present in the arteries, arterioles, capillaries of putamen, globus pallidus, thatalmus and deep cerebellar white matter.	
	Natale	Greater than 2/3 of patients.		
Peripheral neuropathy	Wilson			
	Kubota	47.4% of patients	Demyelinating and axonal	
	Nance and Berry	84.6% of patients	May not be clinically significant	
	Rapin			
	Natale			

Table 3

Relative involvement of different parts of the nervous system by different pathological processes in CS

Location	Neuronal loss	Demyelination	Gliosis	Calcification
Cerebrum	+	+++	++	+++
Cerebellum	+++	+	++	+++
Basal ganglia	+++	–	–	+++
Brainstem	+	++	+	
Spinal cord	–	++	+	–
Peripheral nerves		+++	+	–

Table 4

Diagnostic criteria for CS (modified from Laugel et al.) (Laugel, 2013, p. 167)

	Nance and Berry	**Modified criteria**
Major criteria	Developmental delay	Developmental delay
	Growth failure	Progressive growth failure
		Progressive microcephaly
Minor criteria	Cutaneous photosensitivity	Cutaneous photosensitivity
	Pigmentary retinopathy and/or cataracts	Pigmentary retinopathy and/or cataracts
	Sensorineural hearing loss	Progressive sensorineural hearing loss
	Dental caries	Enamel hypoplasia
	Cachetic dwarfism	Enophthalmia

Table 5

Recommended testing in CS patients

	Test
Vision	Annual eye exam, with fundoscopy. Evaluation for cataracts. Visual evoked potentials may be considered
Hearing	Hearing tests – pure tone/behavioral audiometry. Brainstem evoked potentials may be considered
Other	Liver and renal function tests Regular blood pressure checks Regular blood sugar checks