

# ERCC8-related Cockayne syndrome type-1: A rare entity diagnosed in a Turkish boy

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## Abstract

Cockayne syndrome (CS, OMIM #216400 and OMIM #133540) is a rare, progressive, multisystemic disorder that results in premature aging and cachectic dwarfism. It is an autosomal recessive disorder with a prevalence of 2-2.5 per million. Pathogenic variants detected in the *ERCC excision repair 6 (ERCC6)* and *ERCC excision repair 8 (ERCC8)* genes are responsible for molecular pathogenesis. In this case report, an 11-year-old boy with severe microcephaly, growth retardation, loss of subcutaneous fat tissue, neuromotor developmental delay, bilateral cataracts, and facial dysmorphism but without dermal photosensitivity, who had a novel missense variant in trans configuration with a nonsense variant is presented.

**Keywords:** Cockayne syndrome, ERCC8 gene, novel variant

## Introduction

Cockayne syndrome (CS, OMIM #216400 and OMIM #133540) is an autosomal recessive, multisystemic disorder with a prevalence assumed to be 2–2.5 per million [1]. The main clinical features include microcephaly, growth failure, photosensitivity, developmental delay, cataracts, sensorineural deafness, feeding difficulties, and loss of subcutaneous fat [2]. Three subtypes of CS have been defined based on the clinical expressivity and age of onset of symptoms. In type 1 (classical/moderate), developmental delay and growth failure usually begin in the first 2 years of life. Type 2 is the severe and early-onset form of CS, while type 3 is the mild, late-onset form that may not become apparent until later in childhood [3]. However, the differences between the subtypes are not always clear-cut, and they share a large overlapping spectrum of severity [4]. Most CS cases have increased sensitivity to sunlight because of deficiencies in repairing damaged DNA caused by pathogenic homozygous or compound heterozygous variants in one of two genes: *excision repair cross-complementation 6 (ERCC6)* (also known as CSB) (OMIM # 609413) or *ERCC8* (also known as CSA) (OMIM # 609412). Although increased sensitivity to sunlight is a common feature, it should be kept in mind that microcephaly and postnatal growth failure are the major findings for CS suspicion in any child.

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## Informed Consent

The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

## Conflict of Interest

No conflict of interest was declared by the authors.

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## Case presentation

Our patient was referred to our outpatient clinics by the Pediatric Gastroenterology Department to evaluate dysmorphic features. He was delivered by normal spontaneous vaginal delivery at 36 weeks, resulting in an uneventful pregnancy of non-consanguineous parents. Birth parameters for gestational age were 2360 g (10–25th percentile) and 48 cm (50–75th percentile). He passed the neonatal hearing test. He could sit without support at around 15 months and walk with support at the age of 3. Progressive contractures of the lower extremities developed around age 6, and he became wheelchair-dependent. He could speak only a few words and was diagnosed with bilateral cataracts at the age of 3. His cranial MRI showed posterior fossa dilatation and was reported as a Dandy-Walker malformation variant (Figure 1). Repetitive serum transaminase levels were elevated, so a liver biopsy was performed, which showed non-specific hepatocyte degeneration. Growth hormone replacement therapy was administered at the age of 10 for 1 year, but he did not benefit. At age 11, a physical examination revealed a weight of 11.5 kg (-7.38 SD), a height of 102 cm (-6.6 SD), and an OFC of 45 cm (-6.37 SD). He had deeply set eyes, a prominent nasal bridge, a pointed chin, decreased subcutaneous fat tissue, multiple dental caries, and abnormal-sized and shaped teeth. Thin extremities and spasticity in the lower extremities were noted (Figure 2).

Figure 1: Sagittal T1-weighted MRI of patient showing posterior fossa dilatation.



Figure 2: Facial dysmorphic features of the patient comprising deeply set eyes, prominent nasal bridge and pointy chin.



Karyotype analysis revealed a normal male karyotype. Following standard gDNA extraction methods, *ERCC8* and *ERCC6* genes were sequenced using the Illumina Miseq Inc, USA platform, according to the manufacturer's protocols. The detected

variants were classified according to the Standards and Guidelines for the Interpretation of Sequence Variants released by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology [5]. A novel c.644A>T variant and a rare c.581G>A (rs76598851) variant in the *ERCC8* gene (NM\_000082.3) were detected in the heterozygous state (Figures 3 and 4). Segregation analysis revealed that the c.644A>T allele was paternal, and the c.581G>A variant was of maternal origin. The novel c.644A>T (p.Asp215Val) variant is classified as a "Variant of Uncertain Significance" by ACMG criteria and is assumed to cause rigidification of the protein structure

([http://biosig.unimelb.edu.au/dynamut/results\\_prediction/157676006822](http://biosig.unimelb.edu.au/dynamut/results_prediction/157676006822)) (Figure 5). The c.581G>A (p.Trp194Ter) variant is classified as "Pathogenic"; it is a nonsense variant that leads to premature termination codon and a truncated protein. Informed written consent was obtained from the patient's parents for collecting samples, performing genetic testing, and publishing of patient images.

Figure 3: IGV image of the p.Asp215Val variant detected at the patient.

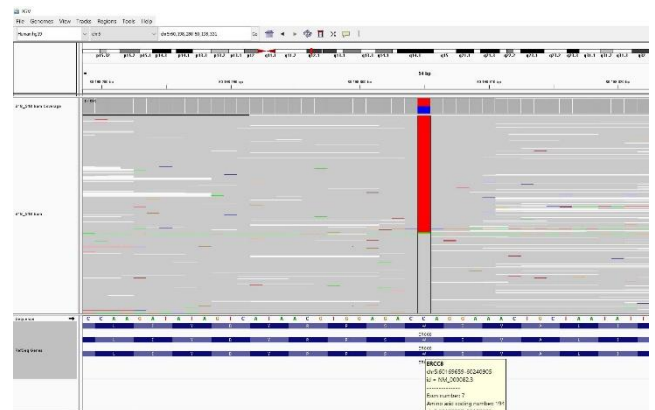


Figure 4: IGV image of the p.Trp194Ter variant detected at the patient.

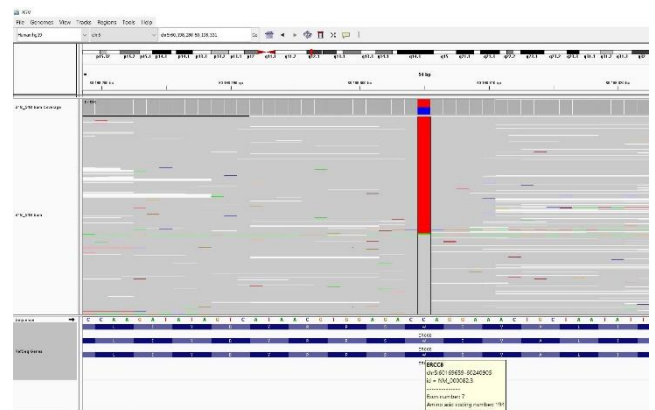
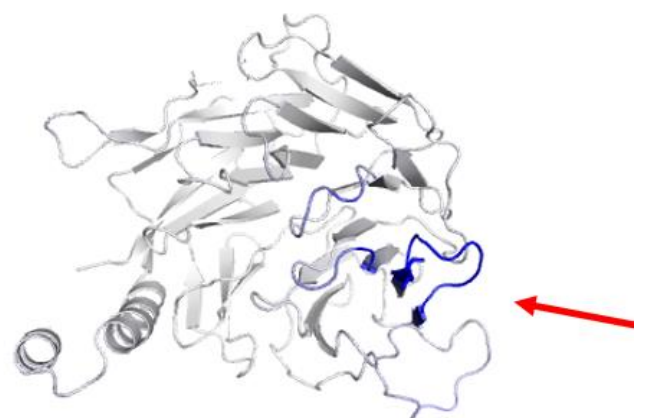


Figure 5: Schematic representation and rigidification site resulting of p.Asp215Val variant at the protein level.



## Discussion

CS is a rare disease that was first reported by Sir Edward A. Cockayne in 1936 in two siblings with progressive hearing loss, retinal atrophy, and dwarfism [6].

Cardinal clinical features such as microcephaly and growth retardation were early descriptions of CS. Nance and Berry first defined the diagnostic criteria for CS with their large series of patients in 1992, and Wilson et al. reported comprehensive CS diagnostic criteria in 2016 [7,8]. More recently, in early 2021, Spitz et al. proposed a new quantitative-based method for establishing the diagnosis in early childhood and severity scoring for appropriate evaluation and surveillance of patients [9]. Due to the heterogeneous nature of the disease, it is believed that the frequency of CS may be lower because of difficulties in diagnosis, especially the reliance on dermal photosensitivity, which is thought to be helpful in diagnosis [10,11]. Although our patient manifested both major criteria of microcephaly and growth retardation, we believe that the age of diagnosis was slightly delayed because he did not manifest cutaneous photosensitivity [8].

The *ERCC8* gene (also known as CSA) is responsible for 35% of patients with the CS phenotype. The reported missense variants of the *ERCC8* gene are mostly located at the WD4 domain of the protein, which is an important component for beta-propeller structures functioning in protein-protein interaction. It has been demonstrated that missense variants located around this region can lead to impaired binding and disruption of the protein structure. However, although missense variants are mostly localized in a hotspot region, phenotype-genotype correlations and clinical heterogeneity still remain elusive among patients [12].

## Conclusion

Cockayne syndrome is a rare neurodevelopmental disorder with multisystemic involvement, and due to the molecular function of the underlying genes, it is known as one of the DNA repair mechanism dysfunction syndromes. Although cutaneous photosensitivity is assumed to be one of the major features of the syndrome, it should be kept in mind that not all patients manifest this cardinal feature. Reporting a novel variant will enrich the clinical and genetic spectrum of CS and provide insight for further genotype-phenotype analysis. In conclusion, diagnosing rare diseases in advance is essential to prevent unnecessary procedures and provide proper counseling for families.

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