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CASE REPORT

A new mutation in the CSB gene in a Chinese patient with mild Cockayne syndrome

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Key Clinical Message

Cockayne syndrome (CS) is a rare autosomal recessive genetic disease characterized by growth failure and progressive neurological degeneration. Here we report a mild form of CS patient who was homozygous for the C526T transition resulting in a new nonsense mutation, which converts Arg176 to a stop codon.

Keywords

Cockayne syndrome, CSB gene, mutation.

Introduction

Cockayne syndrome (CS) is a rare genetic disorder with autosomal recessive inheritance. It is characterized by severe growth retardation, progressive neurological degeneration, and accelerated aging [1]. Associated clinical features of CS patients are gait defects, structural eye abnormalities such as cataracts and progressive pigmentary retinopathy, sensorineural hearing loss, dental caries, and cutaneous photosensitivity. The disease is clinically heterogeneous, with a wide range in type and severity of symptoms.

The phenotypic spectrum of CS can be divided into three general clinical groups: CS type I (moderate CS) is characterized by normal prenatal growth with the normal length, weight, and head circumference. However, the disease would become fully manifest, and the onset of growth and developmental would fall below normal in the first 2 years. Progressive impairment of central and peripheral nervous system function, vision, hearing, dental caries, and photosensitivity leads to severe disability, with death occurring in the first or second decade. CS type II (severe CS or early-onset CS) is evident by growth failure at birth, with little or no postnatal neurological development. Congenital cataracts or other structural anomalies of the eye may be present. Affected individuals have early postnatal contractures of the spine (kyphosis, scoliosis) and joints [2]. CS type II overlaps clinically with the cerebro-oculofacioskeletal syndrome (COFS), which is also referred to as Pena-Shokeir syndrome type II. Cellular defects in the response to ultraviolet (UV) irradiation appear to be similar for type I patients and type II patients. CS type III (mild CS or late-onset CS) is assigned to individuals with some late-onset features of CS, with mostly normal growth and cognitive development [3].

CS belongs to the family of nucleotide excision repair (NER) deficient disorders, together with xeroderma pigmentosum (XP) [4], trichothiodystrophy (TTD), and UV-sensitive syndrome (UVSS). The process of NER protects cells from a wide range of DNA lesions including UV-induced lesions. CS cells are specifically defective in transcription-coupled DNA repair (TCR), a subpathway of NER, which is closely linked to the basal transcription machinery and preferentially targets helix-distorting DNA

lesions in the transcribed DNA strand of active genes. This correlated with earlier findings that RNA synthesis recovered rapidly after UV irradiation of normal cells, whereas this recovery did not occur in CS cells. The other subpathway of NER (global genome repair or GGR) is responsible for the removal of helix-distorting DNA lesions throughout the genome including those from the nontranscribed strand in the active gene. GGR is normally active in CS cells but defective in XP or TTD cells [5].

Classic CS is diagnosed by clinical findings, comprising postnatal growth failure and progressive neurological dysfunction along with other minor criteria [6]. This rare disease is linked to mutations in the CSB/ERCC6 and CSA/ERCC8 genes encoding proteins involved in the TCR pathway. Molecular genetic testing or a specific DNA repair assay on fibroblasts (available only on a research basis) can confirm the diagnosis. Mutations in CSB are distributed along the whole genomic sequence and almost all types of mutations are found, such as short insertions and deletions, nonsense mutations, splice mutations, missense mutations, promoter mutation, and polymorphisms [7, 8].

Here, we report a Chinese patient with a clinical phenotype of mild CS who has a homozygous nonsense mutation in the CSB gene resulting in a new stop codon from the mutation.

Materials and Methods

Case report

The patient was referred at 16 years of age, with tremor of hands, global developmental delay, and abnormal walking gait. A physical examination showed him to be 149 cm (<2 SD) in height and 30 kg in weight (Fig. 1). An examination by the ophthalmologist established that the patient had retinal pigment degeneration. An examination by the otolaryngologist showed that he had bilateral nerve deafness and hearing loss 30–50 dB. He had early old face, long limbs, and his bone age was 19. Otherwise, growth hormone, adrenal hormone, thyroid hormone, and sex hormone appeared normal. A head computed tomography scan showed calcifications of the subcortical white matter and bilateral basal ganglions, leukoencephalopathy and brain atrophy. Brain magnetic resonance imaging revealed demyelination of generalized white matter and dentate nucleus, abnormal signal stove of bilateral basal ganglions. His karyotype was 46, XY.

Sequencing of genomic DNA

Sequence analysis of the ERCC6 gene using genomic DNA from the patient was applied to all 20 exons and the flanking splice junction consensus sequences of the ERCC6 (CSB) gene (by BGI, China) [9].

Figure 1. The patient at 16 years of age, 149 cm tall and 30 kg in weight. He had early old face and long limbs, with tremor of hands, and abnormal walking gait.

Results

The patient was homozygous for three mutations: a nonsense mutation C526T, which converts Arg176 to a stop codon (CGA 526: Arg176 to TGA 526: stop, located at Exon3), and two missense mutations G1196A and C3962G,

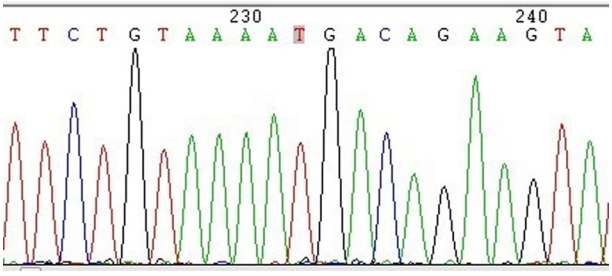

Figure 2. DNA sequence chromatogram (electrophoregram) showing mutations in CS patient. In patient, a C to T homozygous mutation was detected at nucleotide position 526. This C to T transition generates the nonsense codon TGA at amino acid position 176. (CGA 526: Arg176 to TGA 526: stop).

respectively, resulting in the amino acid changes Gly399Asp and Ser1321Cys (Fig. 2). These missense mutations are not relevant for the pathological phenotype since they are located downstream of the nonsense mutation.

Discussion

This study demonstrated for the first time that a mild CS patient resulted from a homozygous nonsense mutation (CGA 526: Arg176 to TGA 526: stop), located at CSB gene exon3. Our findings are consistent with the prior reports that patients with no detectable CSB fared better than patients with slightly truncated CSB. It has been hypothesized that the mutated CSB protein might have some additional inhibitory functions in transcription or in oxidative damage repair, which could specifically lead to the severe CS phenotype. This hypothesis would probably imply that mutated CSB polypeptides had a dominant negative effect, but direct experimental evidence for this inhibitory effect has not been provided yet.

The clinical features of CS, as a rare disorder of DNA repair system, were first described by Cockayne in 1936. Venema et al. [10] first pointed out that CS cells had a defect in TCR of UV-induced DNA damage [11]. The CSB gene, located on chromosome 10q11, encoded a 168-kDa protein of 1493 amino acids. The CSB protein included seven helicase-like ATPase motifs and pertained to the SWI2/SNF2 family of proteins generally involved in chromatin remodeling, transcription, and DNA repair [12]. After irradiation RNA synthesis was depressed in both normal and CS cells, but it recovered rapidly in normal cells and failed in cells from patients with CS. When the ERCC6 cDNA was introduced into different human cell lines, it was able to correct the UV sensitivity and post UV irradiation RNA synthesis defect in a CS-B cell line, CS1AN, and this cell strain was found to contain mutations in the ERCC6 gene [13]. CSB protein has been related to various repair and transcription processes, but the details of these mechanisms remained unclear.

The actual mechanism of CS remained poorly unknown and the great differences between severity and age of onset could still not be observed at the molecular level. The study by Horibata et al. indicated that the very mild clinical presentation of UVSS was due to a homozygous stop mutation at CSB gene position 308 (CGA 308: Arg77 to TGA 308: stop) inducing a severely truncated CSB protein, which contained only the N-terminal 76aa generated in UVs1KO cells. Newman et al. [14] have raised the hypothesis that the fusion protein comprising the first five exons of CSB gene and the open reading frame of a PGBD3 transposon nested in intron 5 could be responsible for the pathogenesis of CS. According to this hypothesis, mutations downstream of CSB exon 5/6 boundary in the ATPase and C-terminal domains would cause CS by impairing expression of the full-length CSB protein without affecting expression of the CSB-PGBD3 fusion protein [14]. However, we found out that a nonsense mutation upstream of exon 6 caused a mild CS phenotype, this molecular research was in sharp contrast with the mild clinical feature presented by the patient, who had slight growth failure and progressive neurological degeneration. Comparatively, the much more severe clinical picture of CSB patients was usually due to apparently milder CSB mutations, such as missense mutations or truncating mutations downstream to position 77 described previously [9].

Genotype–phenotype correlation researches have attempted to state why certain mutations in the same gene are expressed separately, but no such simple, obvious correlations have been proved. In conclusion, it is proposed that carrying a truncated or mutated version of CSB may be highly harmful [15], whereas the complete absence of the product may give rise to mild phenotypes. It is tempting to suppose that an abnormal CSB protein not only completely lost its functional activity but probably also its ability to interact with other cellular proteins, which a normal CSB protein interacts with. It is reasonable to speculate on a direct relation between the severity of symptoms and the length of truncated CSB proteins. Thus, the mildest cases of CS without any detectable protein would stand for one end of the spectrum, and the other end would contain the severest phenotype of CS type II, with mutations impacting import ant functions.

In summary, we report a mild form of CS patient who was homozygous for the C526T transition resulting in a new nonsense mutation, which converts Arg176 to a stop codon. All of these observations are brand new and provide a deeper level of understanding about mechanisms of CS. Therefore, our results will likely provide more specific targets to prevent or improve CS.

Conflict of Interest

None declared.

References

1. Falik-Zaccai, T. C., M. Laskar, N. Kfir, W. Nasser, H. Slor, and M. Khayat. 2008. Cockayne syndrome type II in a Druze isolate in Northern Israel in association with an insertion mutation in ERCC6. Am. J. Med. Genet. A 146A:1423–1429.
2. Colella, S., T. Nardo, D. Mallery, C. Borrone, R. Ricci, G. Ruffa, et al. 1999. Alterations in the CSB gene in three Italian patients with the severe form of Cockayne syndrome (CS) but without clinical photosensitivity. Hum. Mol. Genet. 8:935–941.

3. Rapin, I., K. Weidenheim, Y. Lindenbaum, P. Rosenbaum, S. N. Merchant, S. Krishna, et al. 2006. Cockayne syndrome in adults: review with clinical and pathologic study of a new case. J. Child Neurol. 21: 991–1006.
4. Slor, H., S. Batko, S. G. Khan, T. Sobe, S. Emmert, A. Khadavi, et al. 2000. Clinical, cellular, and molecular features of an Israeli xeroderma pigmentosum family with a frameshift mutation in the XPC gene: sun protection prolongs life. J. Invest. Dermatol. 115:974–980.
5. Laugel, V., C. Dalloz, A. Stary, V. Cormier-Daire, I. Desguerre, M. Renouil, et al. 2008. Deletion of 5′ sequences of the CSB gene provides insight into the pathophysiology of Cockayne syndrome. Eur. J. Hum. Genet. 16:320–327.
6. Mahmoud, A. A., G. M. Yousef, I. Al-Hifzi, and E. P. Diamandis. 2002. Cockayne syndrome in three sisters with varying clinical presentation. Am. J. Med. Genet. 111:81–85.
7. Laugel, V., C. Dalloz, M. Durand, F. Sauvanaud, U. Kristensen, M. C. Vincent, et al. 2010. Mutation update for the CSB/ERCC6 and CSA/ERCC8 genes involved in Cockayne syndrome. Hum. Mutat. 31:113–126.
8. Mallery, D. L., B. Tanganelli, S. Colella, H. Steingrimsdottir, A. J. van Gool, C. Troelstra, et al. 1998. Molecular analysis of mutations in the CSB (ERCC6) gene in patients with Cockayne syndrome. Am. J. Hum. Genet. 62:77–85.
9. Horibata, K., Y. Iwamoto, I. Kuraoka, N. G. Jaspers, A. Kurimasa, M. Oshimura, et al. 2004. Complete absence of Cockayne syndrome group B gene product gives rise to UV-sensitive syndrome but not Cockayne syndrome. Proc. Natl. Acad. Sci. USA 101:15410–15415.
10. Venema, J., L. H. Mullenders, A. T. Natarajan, A. A. van Zeeland, and L. V. Mayne. 1990. The genetic defect in Cockayne syndrome is associated with a defect in repair of UV-induced DNA damage in transcriptionally active DNA. Proc. Natl. Acad. Sci. USA 87:4707–4711.
11. Nance, M. A., and S. A. Berry. 1992. Cockayne syndrome: review of 140 cases. Am. J. Med. Genet. 42:68–84.
12. Licht, C. L., T. Stevnsner, and V. A. Bohr. 2003. Cockayne syndrome group B cellular and biochemical functions. Am. J. Hum. Genet. 73:1217–1239.
13. Troelstra, C., A. van Gool, J. de Wit, W. Vermeulen, D. Bootsma, and J. H. Hoeijmakers. 1992. ERCC6, a member of a subfamily of putative helicases, is involved in Cockayne's syndrome and preferential repair of active genes. Cell 71:939–953.
14. Newman, J. C., A. D. Bailey, H. Y. Fan, T. Pavelitz, and A. M. Weiner. 2008. An abundant evolutionarily conserved CSB-PiggyBac fusion protein expressed in Cockayne syndrome. PLoS Genet. 4:e1000031.
15. Spivak, G. 2004. The many faces of Cockayne syndrome. Proc. Natl. Acad. Sci. USA 101:15273–15274.