Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Cancer Prone Disease Section

Short Communication

De Sanctis-Cacchione Syndrome

Jyoti Kumar

Stanford University, Department of Pathology Stanford, CA; kumarj@stanford.edu

Published in Atlas Database: August 2019

Online updated version : http://AtlasGeneticsOncology.org/Kprones/DeSanctisCacchioneID10109.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/70728/08-2019-DeSanctisCacchioneID10109.pdf
DOI: 10.4267/2042/70728

Abstract

De Sanctis-Cacchione syndrome is an extremely rare disorder characterized by the skin and eye symptoms of xeroderma pigmentosum that occur along with neurological abnormalities, microcephaly, progressive mental retardation, dwarfism, hypogonadism, deafness, ataxia and quadriparesis. This syndrome is the most severe form of XP. It has also been associated with mutations in the ERCC6, XPA, ERCC2 (XPD), and XPC genes, which play roles in the transcription coupled nucleotide excision repair system.

Keywords

Xeroderma Pigmentosum, ERCC6, CSB, XPA, ERCC2, XPD, XPC, neurological abnormalities, dwarfism, hypogonadism

Identity

This syndrome is the most severe form of xeroderma pigmentosum (XP) (Atlas ID #10004).

Inheritance

Autosomal recessive

Clinics

Phenotype and clinics

De Sanctis-Cacchione syndrome is characterized by the skin and eye symptoms of XP along with neurological symptoms and growth delays. The severity of the clinical presentations varies depending on the nature of the mutation and amount of sun exposure. The earliest skin conditions include persistent erythema, increased freckling and blistering that occur after exposure to sunlight. In most cases, onset of these symptoms is often during infancy, although symptoms may not be apparent until later in childhood in rare cases. Additional skin symptoms include hyperpigmentation, hypopigmentation, or complete depigmentation.

Some patients may develop premalignant lesions such as actinic keratoses. These patients may experience an early onset of skin cancer.

For example, skin cancers such as malignant melanoma, basal cell carcinoma, and squamous cell carcinoma often occur, and the most commonly affected areas are the head, neck, and face.

In De Sanctis-Cacchione syndrome, some of the eye symptoms associated with XP may be present, such as photophobia, keratitis, or conjunctivitis. The severity of symptoms related to the skin and eyes may depend on the amount of exposure to ultraviolet light.

Most patients with De Sanctis-Cacchione syndrome usually have one or more neurological abnormalities with the most frequent being mental retardation.

Other abnormalities may include microcephaly, sensorineural deafness, dysarthria, areflexia, hyporeflexia, or spasticity.

Affected individuals may also demonstrate ataxia or choreoathetosis.

Shortening of the Achilles tendon can lead to quadriparesis.

Individuals with De Sanctis-Cacchione syndrome will also exhibit unusually slow development, profound growth delays resulting in dwarfism and hypogonadism.

Differential Diagnosis

Xeroderma pigmentosum: Typically, XP patients have a similar skin presentation as noted above. However, De Sanctis-Cacchione syndrome is the rarest manifestations of XP with the most severe DNA repair impairment. XP can also present with some neurologic manifestations; however, short

stature and delayed gonadal maturation are more typical of De Sanctis-Cacchione syndrome. The presence of progressive neurologic involvement and age at symptom onset correlate with the degree of DNA repair impairment present (Rahbar 2015).

Cockayne syndrome: Patients have a typical face phenotype (microcephaly, wizened face, deep-set eyes, mandible prognathism, hypoplastic teeth, and malformed ears) and develop dwarfism, hypogonadism, and neurological abnormalities similar to De Sanctis-Cacchione syndrome that include progressive impairment of vision, hearing and speech, behavioral changes, intellectual disability, and ataxia, leading to severe disability (Uribe-Bojanini 2017). However, cases of De Sanctis-Cacchione syndrome can be distinguished from Cockayne syndrome since patients with Cockayne syndrome do not show XP-type skin findings or have increased risk of skin cancer. Conversely, patients with Cockayne syndrome tend to have normal or increased deep tendon reflexes or signs of primary demyelination (Moriwaki 1996).

Although the diagnosis of De Sanctis-Cacchione syndrome can be suspected by the patient's clinical presentation, molecular genetic testing is recommended for confirmation of the patient's mutation and complementation group characterization. The nucleotide excision repair (NER) system includes seven complementation groups XP-A to XP-G in addition to the XP variant group. NER is responsible for repairing UV-induced photoproducts inside DNA. If a mutation is present in any of the components of the pathway, then the entire pathway fails to function normally. Thus, identification of the patient's mutation and complementation group characterization plays an important role in genetic counseling, antenatal diagnosis, discussion of etiology, and the probability of occurrence in future generations (Uribe-Bojanini 2017).

Neoplastic risk

Patients have a 10,000-fold increase in the risk of developing skin basal cell carcinoma and squamous cell carcinoma and a 2,000-fold increased risk of melanoma (Uribe-Bojanini 2017).

Treatment

Total protection of the skin from sunlight is important to prevent the development of skin lesions. Protective methods include use of topical sunscreens, sunglasses, and photoprotective layers of clothing. For the treatment of established skin lesions, chemotherapeutic agents, such as 5-fluorouracil, immunomodulators and retinoids, can be used depending on the location, severity and extension of the lesion (Caldas 2013).

Vitamin D supplementation may be necessary due to deficiency from rigorous sun protection. Psychological advisory and support groups are very important for patients and their families. The management of patients with neurological abnormalities includes the use of hearing aid devices, along with physical, occupational, and speech therapy. Genetic counseling should be offered for families at risk. (Uribe-Bojanini 2017).

Prognosis

The prognosis of the disease is poor overall.

Genes involved and proteins

The nucleotide excision repair (NER) system includes seven complementation groups XP-A to XP-G in addition to the XP variant group. NER is responsible for repairing UV-induced photoproducts inside DNA. If a mutation is present in any of the components of the pathway, then the entire pathway fails to function normally. Patients with De Sanctis-Cacchione syndrome have been found to harbor mutations in ERCC6 (CSB), XPA, ERCC2 (XPD), and XPC genes.

ERCC6 (excision repair cross-complementing rodent repair deficiency, group 6)

Alias

CSB (Cockayne syndrome B), CKN2, ARMD5, RAD26

Location 10q11.23

DNA/RNA

Description

90 kbp; at least 21 exons

Protein

The ERCC6 gene encodes the CSB protein.

Description

1493-amino acid protein has an N-terminal domain, followed by an acidic stretch, a glycine-rich region, a central helicase domain, and a nuclear localization signal (Troelstra et al. 1992).

Expression

Ubiquitous.

Localisation

Nuclear.

Function

Encodes a DNA-binding protein (CSB) that plays a role in transcription-coupled excision repair. The encoded protein has ATP-stimulated ATPase activity, interacts with several transcription and excision repair proteins, and may promote complex formation at DNA repair sites (Troelstra et al. 1992). CSB is essential for the NER system, which removes RNA polymerase blocking lesions. The CSB protein plays an important role in general nuclear

transcription and stimulates RNA polymerase II progression beyond pause sites (Shehata 2014).

Mutations

Germinal
Biallelic mutations have been found in the ERCC6 genomic DNA (C2282T) of three patients with De Sanctis-Cacchione syndrome.

XPA (Xeroderma pigmentosum, complementation group A)

Alias
XP-A, xeroderma pigmentosum, complementation group A, XP1, XPA_HUMAN, XPAC

Location 9q22.33

DNA/RNA

Description
22448 bp; 6 exons.

Protein

Description
273 amino acids, 31.4 kDa. DNA excision repair protein. The functional domain for damaged DNA recognition contains a zinc-finger motif with 4 cysteine residues: Cys-X2-Cys-X17-Cys-X2-Cys motif and a glutamic acid cluster encoded by Exon 2. The nuclear localization signal is located in Exon 1.

Expression
Ubiquitous.

Localisation
Nuclear.

Function
Initiates DNA repair by binding to damaged sites with various affinities, depending on the chemical structure of the lesion. Two proteins have been identified and implicated in one of the first steps of NER system to recognize lesions in DNA: the XPA gene product and the XPC gene product. In vitro the XPA protein binds preferentially to damaged DNA compared to non-damaged DNA. The XPA protein binds to replication protein A (RPA) which enhances the affinity of XPA for damaged DNA and is essential for NER. The XPA protein has been shown to bind to ERCC1 and TFIIH. It is possible that the complex XPA/RPA may inform the repair machinery which strand contains the damage and be eliminated.

Mutations

Germinal
13 nucleotide substitutions and 5 small insertion/deletion.

ERCC2 (Excision repair cross-complementing rodent repair deficiency, complementation group 2)

Alias
XPD, XP-D, xeroderma pigmentosum complementary group D

Location 19q13.32

DNA/RNA

Description
54336 bp; 23 exons

Transcription
2400b mRNA

Protein

Description
760 amino acids.

Expression
Ubiquitous.

Localisation
Nuclear.

Function
5'-3' ATP-dependent helicase activity involved in DNA NER pathway and as a subunit of the basal transcription factor TFIIH.
The ERCC2 (XPD) as the ERCC3 (XPB) protein are also found in the transcription factor TFIIH, a large complex involved in the initiation of transcription. TFIIH fulfills a dual role in transcription initiation and NER and the role of TFIIH in NER might closely mimic its role in the transcription initiation process. In transcription initiation, TFIIH is thought to be involved in unwinding of the promoter site and to allow promoter clearance. In the NER process, TFIIH causes unwinding of the damaged region that has been localized by XPC- RAD23B (HR23B) and XPA-RPA, enabling the accumulation of NER proteins around the damaged site.

Mutations

Germinal
17 mutated sites.

XPC (xeroderma pigmentosum, complementation group C)

Alias
XP-C, XPCC, RAD4, xeroderma pigmentosum, complementation group C

Location 3p25.1

DNA/RNA

Description
17703 bp; 16 exons.

Transcription
3558b mRNA.

Protein

Description
939 amino acids.

Expression
Ubiquitous.

Localisation
Nuclear.

Function
Involved in the early recognition of DNA damage present in chromatin. Two proteins have been identified and implicated in (one of) the first steps of NER system to recognize lesions in DNA: the XPA gene product and the XPC gene product in complex with HR23B. The XPC-HR23B complex has been implicated in DNA damage recognition, especially the cyclobutane pyrimidine dimers induced by UV-light. XPC cells have low NER capacity, but the residual repair has been shown to occur specifically in transcribed genes. It is very likely that the XPC-HR23B complex is the principal damage recognition complex. Binding of XPC-HR23B to a DNA lesion causes local unwinding, so that the XPA protein can bind and the whole repair machinery can be loaded onto the damaged site. The XPC-HR23B complex is only required for global genome repair. In case of transcription coupled repair when an RNA polymerase is stalled at a lesion, the DNA is unwound by the transcription complex and XPA can bind independently of the XPC-HR23B complex.

Mutations

Germinal
A novel germline mutation in the XPC gene (c.547A>T) was identified in one case causing De Sanctis-Cacchione syndrome. This variant is predicted to result in premature protein termination

(p.Lys183*) (Uribe-Bojanini 2017).

References

Caldas AL, Rodrigues MM. De Sanctis-Cacchione syndrome in a female infant--case report. An Bras Dermatol. 2013 Nov-Dec;88(6):979-81

Colella S, Nardo T, Botta E, Lehmann AR, Stefanini M. Identical mutations in the CSB gene associated with either Cockayne syndrome or the DeSanctis-cacchione variant of xeroderma pigmentosum. Hum Mol Genet. 2000 May 1;9(8):1171-5

Moriwaki S, Stefanini M, Lehmann AR, Hoeijmakers JH, Robbins JH, Rapin I, Botta E, Tanganelli B, Vermeulen W, Broughton BC, Kraemer KH. DNA repair and ultraviolet mutagenesis in cells from a new patient with xeroderma pigmentosum group G and cockayne syndrome resemble xeroderma pigmentosum cells. J Invest Dermatol. 1996 Oct;107(4):647-53

Rahbar Z, Naraghi M. De Sanctis-Cacchione syndrome: A case report and literature review. Int J Womens Dermatol. 2015 Aug;1(3):136-139

Shehata L, Simeonov DR, Raams A, Wolfe L, Vanderver A, Li X, Huang Y, Garner S, Boerkoel CF, Thurm A, Herman GE, Tifft CJ, He M, Jaspers NG, Gahl WA. ERCC6 dysfunction presenting as progressive neurological decline with brain hypomyelination. Am J Med Genet A. 2014 Nov;164A(11):2892-900

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 Dec 11;71(6):939-53

Uribe-Bojanini E, Hernandez-Quiceno S, Cock-Rada AM. Xeroderma Pigmentosum with Severe Neurological Manifestations/De Sanctis-Cacchione Syndrome and a Novel XPC Mutation. Case Rep Med. 2017;2017:7162737

Wong HK, Muftuoglu M, Beck G, Imam SZ, Bohr VA, Wilson DM 3rd. Cockayne syndrome B protein stimulates apurinic endonuclease 1 activity and protects against agents that introduce base excision repair intermediates Nucleic Acids Res 2007;35(12):4103-13

This article should be referenced as such:

Kumar J. De Sanctis-Cacchione Syndrome. Atlas Genet Cytogenet Oncol Haematol. 2020; 24(5):217-221.