ERCC3 gene

ERCC excision repair 3, TFIIH core complex helicase subunit

Normal Function

The *ERCC3* gene provides instructions for making a protein called XPB. This protein is an essential part (subunit) of a group of proteins known as the general transcription factor 2 H (TFIIH) complex. The TFIIH complex has two major functions: it is involved in a process called gene transcription, and it helps repair damaged DNA.

Gene transcription is the first step in protein production. By controlling gene transcription, the TFIIH complex helps regulate the activity of many different genes. Studies suggest that the XPB protein works together with XPD, another protein in the TFIIH complex that is produced from the *ERCC2* gene, to start (initiate) gene transcription.

The TFIIH complex also plays an important role in repairing damaged DNA. DNA can be damaged by ultraviolet (UV) rays from sunlight and by toxic chemicals, such as those found in cigarette smoke. DNA damage occurs frequently, but normal cells are usually able to fix it before it can cause problems.

One of the major mechanisms that cells use to fix DNA is known as nucleotide excision repair (NER). As part of this repair mechanism, the TFIIH complex unwinds the section of double-stranded DNA that surrounds the damage. Studies suggest that the XPB protein may act as a wedge, holding open the two strands of DNA so other proteins can snip out (excise) the abnormal section and replace the damaged area with the correct DNA.

Health Conditions Related to Genetic Changes

Trichothiodystrophy

At least one variant (also called a mutation) in the *ERCC3* gene appears to be a rare cause of trichothiodystrophy. This condition affects many parts of the body. The hallmark of trichothiodystrophy is hair that is sparse and easily broken.The *ERCC3* gene variant causes the photosensitive form of the condition, which is characterized by an extreme sensitivity to UV rays from sunlight.

The *ERCC3* gene variant known to cause trichothiodystrophy changes one protein building block (amino acid) in the XPB protein; specifically, it replaces the amino acid

threonine with the amino acid proline at protein position 119 (written as Thr119Pro or T119P) . This variant probably makes the TFIIH complex unstable and reduces its ability to repair DNA damage caused by UV radiation. These problems with DNA repair cause people with the photosensitive form of trichothiodystrophy to be extremely sensitive to sunlight. Other features of the condition, such as slow growth, intellectual disability, and brittle hair, likely result from problems with the transcription of genes needed for normal development before and after birth.

Unlike xeroderma pigmentosum (described below), trichothiodystrophy is not associated with an increased risk of skin cancer. Researchers are working to determine why some variants in the *ERCC3* gene affect a person's cancer risk and others do not.

Xeroderma pigmentosum

At least one variant in the *ERCC3* gene also appears to be a rare cause of xeroderma pigmentosum. This condition is characterized by an extreme sensitivity to UV rays from sunlight. This condition mostly affects the eyes and areas of skin exposed to the sun.

The *ERCC3* gene variant that causes xeroderma pigmentosum changes one amino acid in the XPB protein. Specifically, the variant replaces the amino acid phenylalanine with the amino acid serine at protein position 99 (written as Phe99Ser or F99S). This variant greatly reduces the ability of the TFIIH complex to repair damaged DNA. As damage builds up in DNA, cells malfunction and eventually become cancerous or die.

Problems with DNA repair cause people with xeroderma pigmentosum to be extremely sensitive to UV rays. When UV rays damage genes that control cell growth and division, cells can grow too fast and in an uncontrolled way. As a result, people with xeroderma pigmentosum have a greatly increased risk of developing cancer. These cancers occur most frequently in areas of the body that are exposed to the sun, such as the skin and eyes.

In addition to sun sensitivity, xeroderma pigmentosum is sometimes associated with progressive neurological abnormalities. In affected individuals with the Phe99Ser variant, neurological abnormalities have been relatively mild and have included hearing loss and poor coordination. Studies suggest that the neurological abnormalities associated with this condition result from a buildup of DNA damage, although the brain is not exposed to UV rays. Researchers suspect that other factors damage DNA in nerve cells. It is unclear why some people with xeroderma pigmentosum develop neurological abnormalities and others do not.

Other disorders

Several variants in the *ERCC3* gene can cause features of both xeroderma pigmentosum and another condition related to defective DNA repair called Cockayne syndrome. When this combination of features occurs in the same individual, it is known as xeroderma pigmentosum/Cockayne syndrome (XP/CS) complex. People with XP/CS complex may have extreme sun sensitivity, an increased risk of skin cancer, short stature, hearing loss, poor coordination, and intellectual disability.

Researchers are uncertain how variants in this single gene can cause several different disorders with a wide variety of signs and symptoms. Studies suggest that different *ERCC3* gene variants affect the stability and function of the TFIIH complex in different ways. These variations may account for the different features of xeroderma pigmentosum, trichothiodystrophy, and XP/CS complex.

Other Names for This Gene

- basic transcription factor 2 89 kDa subunit
- BTF2
- BTF2 p89
- DNA excision repair protein ERCC-3
- DNA repair protein complementing XP-B cells
- ERCC3_HUMAN
- excision repair cross-complementation group 3
- excision repair cross-complementing rodent repair deficiency, complementation group 3
- excision repair cross-complementing rodent repair deficiency, complementation group 3 (xeroderma pigmentosum group B complementing)
- GTF2H
- RAD25
- TFIIH 89 kDa subunit
- TFIIH basal transcription factor complex 89 kDa subunit
- TFIIH basal transcription factor complex helicase XPB subunit
- TFIIH p89
- xeroderma pigmentosum group B-complementing protein
- xeroderma pigmentosum, complementation group B

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of ERCC3 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2071[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28ERCC3%5BTIAB%5D%29+OR+%28XPB%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- ERCC EXCISION REPAIR 3, TFIIH CORE COMPLEX HELICASE SUBUNIT; ERCC3 (https://omim.org/entry/133510)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/2071)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=ERCC3[gene])

References

- Coin F, Oksenych V, Egly JM. Distinct roles for the XPB/p52 and XPD/ p44subcomplexes of TFIIH in damaged DNA opening during nucleotide excision repair.Mol Cell. 2007 Apr 27;26(2):245-56. doi: 10.1016/j.molcel.2007.03.009. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17466626)
- Lambert WC, Gagna CE, Lambert MW. Xeroderma pigmentosum: its overlap withtrichothiodystrophy, Cockayne syndrome and other progeroid syndromes. Adv Exp MedBiol. 2008;637:128-37. doi: 10.1007/978-0-387-09599-8_14. No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/19181118)
- Oh KS, Imoto K, Boyle J, Khan SG, Kraemer KH. Influence of XPB helicase onrecruitment and redistribution of nucleotide excision repair proteins at sites ofUV-induced DNA damage. DNA Repair (Amst). 2007 Sep 1;6(9):1359-70. doi:10.1016/j.dnarep.2007.03.025. Epub 2007 May 16. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/17509950) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3471374/)
- Oh KS, Khan SG, Jaspers NG, Raams A, Ueda T, Lehmann A, Friedmann PS, EmmertS, Gratchev A, Lachlan K, Lucassan A, Baker CC, Kraemer KH. Phenotypicheterogeneity in the XPB DNA helicase gene (ERCC3): xeroderma pigmentosum withoutand with Cockayne syndrome. Hum Mutat. 2006 Nov;27(11):1092-103. doi:10.1002/humu.20392. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/16947863)
- Oksenych V, Coin F. The long unwinding road: XPB and XPD helicases in damagedDNA opening. Cell Cycle. 2010 Jan 1;9(1):90-6. doi: 10.4161/cc.9.1.10267. Epub2010 Jan 5. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/20016270)
- Riou L, Zeng L, Chevallier-Lagente O, Stary A, Nikaido O, Taieb A, Weeda G, Mezzina M, Sarasin A. The relative expression of mutated XPB genes results inxeroderma pigmentosum/Cockayne's syndrome or trichothiodystrophy cellularphenotypes. Hum Mol Genet. 1999 Jun;8(6):1125-33. doi: 10.1093/hmg/8.6.1125. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/10332046)
- Weeda G, Eveno E, Donker I, Vermeulen W, Chevallier-Lagente O, Taieb A, StaryA, Hoeijmakers JH, Mezzina M, Sarasin A. A mutation in the XPB/ERCC3 DNA repairtranscription gene, associated with trichothiodystrophy. Am J Hum Genet. 1997Feb;60(2):320-9. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/901240

5) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1712398/)

- Weeda G, van Ham RC, Vermeulen W, Bootsma D, van der Eb AJ, Hoeijmakers JH. Apresumed DNA helicase encoded by ERCC-3 is involved in the human repair disordersxeroderma pigmentosum and Cockayne's syndrome. Cell. 1990 Aug 24;62(4):777-91.doi: 10.1016/0092-8674(90)90122-u. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/2167179)

Genomic Location

The *ERCC3* gene is found on chromosome 2 (https://medlineplus.gov/genetics/chromosome/2/).

Last updated April 6, 2023