ERCC3 Gene

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1. 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 IIH (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 the sun and by toxic chemicals, radiation, and unstable molecules called free radicals. 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.

2. Health Conditions Related to Genetic Changes

2.1 Trichothiodystrophy

Mutations in the *ERCC3* gene appear to be a rare cause of trichothiodystrophy. At least one mutation in this gene can cause the photosensitive form of the condition, which is characterized by an extreme sensitivity to UV rays from sunlight.

The single *ERCC3* gene mutation 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 mutation probably makes the TFIIH complex unstable and reduces its ability to repair DNA damage caused by UV radiation. 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 mutations in the *ERCC3* gene affect a person's cancer risk and others do not.

2.2 Xeroderma Pigmentosum

Mutations in the *ERCC3* gene also appear to be a rare cause of xeroderma pigmentosum. A single *ERCC3* gene mutation has been identified in people with this condition. This mutation changes one protein building block (amino acid) in the XPB protein; specifically, it replaces the amino acid phenylalanine with the amino acid serine at protein position 99 (written as Phe99Ser or F99S). This mutation greatly reduces the ability of the TFIIH complex to repair damaged DNA. As a result, abnormalities accumulate in DNA, causing cells to malfunction and eventually to become cancerous or die. These problems with DNA repair cause people with xeroderma pigmentosum to be extremely sensitive to UV rays from sunlight.

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 mutation, 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 can damage DNA in nerve cells. It is unclear why some people with xeroderma pigmentosum develop neurological abnormalities and others do not.

2.3 Other disorders

Several mutations 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. The signs and symptoms of XP/CS complex include extreme sun sensitivity, an increased risk of skin cancer, short stature, hearing loss, poor coordination, and intellectual disability.

Researchers are uncertain how mutations in this single gene can cause several different disorders with a wide variety of signs and symptoms. Studies suggest that different *ERCC3* gene mutations 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.

3. 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
- XPB

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