

# ERCC2 Gene

Subjects: Genetics & Heredity

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ERCC excision repair 2, TFIIH core complex helicase subunit

Keywords: genes

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## 1. Normal Function

The *ERCC2* gene provides instructions for making a protein called XPD. 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. The XPD protein appears to stabilize the TFIIH complex. Studies suggest that the XPD protein works together with XPB, another protein in the TFIIH complex that is produced from the *ERCC3* 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 separates the section of double-stranded DNA that surrounds the damage. The XPD protein helps with this process by acting as a helicase, which is an enzyme that attaches to particular regions of DNA and temporarily unwinds the two spiral strands. Once the damaged region has been exposed, other proteins 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

At least 20 mutations in the *ERCC2* gene have been found to cause trichothiodystrophy. Mutations in this gene are the most common cause of the photosensitive form of the condition, which is characterized by an extreme sensitivity to UV rays from sunlight.

Studies suggest that the *ERCC2* gene mutations responsible for trichothiodystrophy reduce the amount of functional TFIIH complex in cells. Without enough of this complex, cells cannot effectively 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, probably 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 *ERCC2* gene affect a person's cancer risk and others do not.

### 2.2 Xeroderma Pigmentosum

More than two dozen mutations in the *ERCC2* gene have been identified in people with xeroderma pigmentosum. Mutations in this gene are the second most common cause of xeroderma pigmentosum in the United States.

The *ERCC2* gene mutations responsible for xeroderma pigmentosum prevent the TFIIH complex from repairing damaged DNA effectively. 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.

When xeroderma pigmentosum is caused by *ERCC2* gene mutations, it is often associated with progressive neurological abnormalities. These nervous system problems include hearing loss, poor coordination, difficulty walking, movement problems, loss of intellectual function, difficulty swallowing and talking, and seizures. The neurological abnormalities are thought to 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.

## 2.3 Other Disorders

Rarely, mutations in the *ERCC2* gene can cause features of both xeroderma pigmentosum and trichothiodystrophy in the same individual. This condition is known as xeroderma pigmentosum/trichothiodystrophy (XP/TTD) complex. *ERCC2* gene mutations have also been identified in a few individuals with signs and symptoms of both xeroderma pigmentosum and another condition related to defective DNA repair called Cockayne syndrome. This combination of features is known as xeroderma pigmentosum/Cockayne syndrome (XP/CS) complex.

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 *ERCC2* gene mutations affect the stability and function of the TFIIH complex in different ways. Mutations also have varied effects on the interaction between the XPD protein and other proteins that make up the TFIIH complex. These variations may account for the different features of xeroderma pigmentosum, trichothiodystrophy, and XP/TTD and XP/CS complexes.

## 3. Other Names for This Gene

- basic transcription factor 2 80 kDa subunit
- BTF2 p80
- COFS2
- CXPB
- DNA excision repair protein ERCC-2
- DNA repair protein complementing XP-D cells
- EM9
- ERCC2\_HUMAN
- excision repair cross-complementation group 2
- excision repair cross-complementing rodent repair deficiency, complementation group 2
- MAG
- MGC102762
- MGC126218
- MGC126219
- TFIIH
- TFIIH 80 kDa subunit
- TFIIH basal transcription factor complex 80 kDa subunit
- TFIIH basal transcription factor complex helicase subunit
- TFIIH p80

- TTD
- xeroderma pigmentosum complementary group D
- xeroderma pigmentosum group D-complementing protein
- XPD

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