ERCC2 gene

ERCC excision repair 2, TFIIH core complex helicase subunit

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 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. 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 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). The TFIIH complex is part of this repair mechanism. The XPD protein acts as a helicase, which is an enzyme that attaches (binds) 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.

Health Conditions Related to Genetic Changes

Trichothiodystrophy

Many variants (also called mutations) in the *ERCC2* gene have been found to cause trichothiodystrophy. This condition affects many parts of the body. The hallmark of trichothiodystrophy is hair that is sparse and easily broken. Affected children may develop severe hip degeneration.

Variants 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 variants 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 another condition called 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 *ERCC2* gene affect a person's cancer risk and others do not.

Xeroderma pigmentosum

More than two dozen variants in the *ERCC2* gene have been identified in people with 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.

Variants in the *ERCC2* gene are the second most common cause of xeroderma pigmentosum in the United States. The *ERCC2* gene variants responsible for xeroderma pigmentosum prevent the TFIIH complex from repairing damaged DNA effectively. As damage builds up in DNA, cells malfunction and eventually become cancerous or die. These 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.

When xeroderma pigmentosum is caused by *ERCC2* gene variants, 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.

Other disorders

Rarely, variants 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 variants 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 variants in this single gene can cause several different disorders with a wide variety of signs and symptoms. Studies suggest that different *ERCC2* gene variants affect the stability and function of the TFIIH complex in different ways. Variants also have varied effects on the interaction between the XPD protein and other proteins that make up the TFIIH complex. These variants may account for the different features of xeroderma pigmentosum, trichothiodystrophy, and XP/TTD and XP/CS complexes.

Other Names for This Gene

- basic transcription factor 2 80 kDa subunit
- BTF2 p80
- COFS2
- CXPD
- 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

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of ERCC2 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=2068[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28ERCC2%5BTIAB%5D%29+OR+%28XPD%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- ERCC EXCISION REPAIR 2, TFIIH CORE COMPLEX HELICASE SUBUNIT; ERCC2 (https://omim.org/entry/126340)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/2068)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=ERCC2[gene])

References

- Boyle J, Ueda T, Oh KS, Imoto K, Tamura D, Jagdeo J, Khan SG, Nadem C, Digiovanna JJ, Kraemer KH. Persistence of repair proteins at unrepaired DNAdamage distinguishes diseases with ERCC2 (XPD) mutations: cancer-prone xerodermapigmentosum vs. non-cancer-prone trichothiodystrophy. Hum Mutat. 2008Oct;29(10):1194-208. doi: 10.1002/humu.20768. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18470933) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3477783/)
- Broughton BC, Berneburg M, Fawcett H, Taylor EM, Arlett CF, Nardo T, StefaniniM, Menefee E, Price VH, Queille S, Sarasin A, Bohnert E, Krutmann J, Davidson R, Kraemer KH, Lehmann AR. Two individuals with features of both xerodermapigmentosum and trichothiodystrophy highlight the complexity of the clinicaloutcomes of mutations in the XPD gene. Hum Mol Genet. 2001 Oct 15;10(22): 2539-47.doi: 10.1093/hmg/10.22.2539. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/11709541)
- DiGiovanna JJ, Kraemer KH. Shining a light on xeroderma pigmentosum. J InvestDermatol. 2012 Mar;132(3 Pt 2):785-96. doi: 10.1038/jid.2011.426. Epub 2012 Jan5. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/22217736)
- DiGiovanna JJ, Randall G, Edelman A, Allawh R, Xiong M, Tamura D, Khan SG, Rizza ERH, Reynolds JC, Paul SM, Hill SC, Kraemer KH. Debilitating hipdegeneration in trichothiodystrophy: Association with ERCC2/XPD mutations, osteosclerosis, osteopenia, coxa valga, contractures, and osteonecrosis. Am J MedGenet A. 2022 Dec;188(12):3448-3462. doi: 10.1002/ajmg.a.62962. Epub 2022 Sep 14. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/36103153)

- Faghri S, Tamura D, Kraemer KH, Digiovanna JJ. Trichothiodystrophy: asystematic review of 112 published cases characterises a wide spectrum ofclinical manifestations. J Med Genet. 2008 Oct;45(10):609-21. doi:10.1136/jmg.2008.058743. Epub 2008 Jun 25. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18603627) or Free article on PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3459585/)
- 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)
- Lehmann AR. The xeroderma pigmentosum group D (XPD) gene: one gene, twofunctions, three diseases. Genes Dev. 2001 Jan 1;15(1):15-23. doi:10.1101/gad.859501. No abstract available. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/11156600)
- Nishiwaki T, Kobayashi N, Iwamoto T, Yamamoto A, Sugiura S, Liu YC, Sarasin A, Okahashi Y, Hirano M, Ueno S, Mori T. Comparative study of nucleotide excisionrepair defects between XPD-mutated fibroblasts derived from trichothiodystrophyand xeroderma pigmentosum patients. DNA Repair (Amst). 2008 Dec 1;7(12):1990-8.doi: 10.1016/j.dnarep.2008.08.009. Epub 2008 Oct 10. Citation on PubMed (https://pubmed.ncbi.nlm.nih.gov/18817897)
- 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)
- Zhou X, Khan SG, Tamura D, Ueda T, Boyle J, Compe E, Egly JM, DiGiovanna JJ, Kraemer KH. Abnormal XPD-induced nuclear receptor transactivation in DNA repairdisorders: trichothiodystrophy and xeroderma pigmentosum. Eur J Hum Genet. 2013Aug;21(8):831-7. doi: 10.1038/ejhg.2012.246. Epub 2012 Dec 12. Citation on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/23232694)

Genomic Location

The *ERCC2* gene is found on chromosome 19 (https://medlineplus.gov/genetics/chromosome/19/).

Last updated April 6, 2023