IKBKG gene

inhibitor of nuclear factor kappa B kinase regulatory subunit gamma

Normal Function

The *IKBKG* gene provides instructions for producing one piece (subunit) of the IKK protein complex, which is a group of related proteins that regulates the activity of nuclear factor-kappa-B. Nuclear factor-kappa-B is a protein complex that binds to DNA and controls the activity of other genes.

When the IKK protein complex is in the resting state (inactive), nuclear factor-kappa-B and the IKK complex are attached (bound) together. In response to certain chemical signals, the IKK complex releases nuclear factor-kappa-B.

The IKBKG protein plays a regulatory role in the IKK complex. Once the IKBKG protein is turned on (activated), it activates the other proteins in the complex, which in turn releases nuclear factor-kappa-B. The loose nuclear factor-kappa-B then moves into the nucleus of the cell and binds to DNA.

Nuclear factor-kappa-B regulates the activity of multiple genes, including genes that control the body's immune responses and inflammatory reactions. Nuclear factor-kappa-B also appears to play a role in the signaling pathway that is critical for the formation of ectodermal tissues, including the skin, hair, teeth, and sweat glands. In addition, it protects the cell from certain signals that would otherwise cause it to self-destruct (undergo apoptosis).

Health Conditions Related to Genetic Changes

Anhidrotic ectodermal dysplasia with immune deficiency

Variants (also called mutations) in the *IKBKG* gene have been found to cause anhidrotic ectodermal dysplasia with immune deficiency (EDA-ID). EDA-ID is a condition characterized by the abnormal development of ectodermal tissues. In addition, people with EDA-ID often get infections because their immune system does not function well.

The *IKBKG* gene variants that cause EDA-ID impair the function of the IKBKG protein but do not completely eliminate its ability to regulate nuclear factor-kappa-B. These changes disrupt certain signaling pathways within immune cells and the cells that form ectodermal tissues. This impairs the immune system and disrupts the development of ectodermal tissues.

The severity of the signs and symptoms of EDA-ID depends on the amount of functional IKBKG protein the person has. People with more functional protein typically have milder forms of the disease.

Some people with EDA-ID have unusually dense bones (osteopetrosis) and swelling of soft tissues (lymphedema). This is sometimes referred to as OL-EDA-ID; the acronym is derived from each of the major features of the disorder. It is unclear how variants in the *IKBKG* gene contribute to osteopetrosis and lymphedema in people with OL-EDA-ID.

Incontinentia pigmenti

Variants in the *IKBKG* gene have been identified in people with incontinentia pigmenti, a condition characterized by skin, tooth, and nail abnormalities and an increased risk of stroke and vision loss.

The most common *IKBKG* gene variant that causes incontinentia pigmenti is a complex rearrangement that deletes some genetic material from the *IKBKG* gene. This change accounts for more than 60 to 80 percent of all cases of the condition. This change probably leads to the production of an abnormally small, nonfunctional version of the IKBKG protein.

Other *IKBKG* gene variants that cause incontinentia pigmenti prevent the production of any IKBKG protein. Without this protein, nuclear factor-kappa-B cannot be activated. Cells without active nuclear factor-kappa-B are more sensitive to signals that trigger them to self-destruct. The resulting abnormal cell death likely leads to the signs and symptoms of incontinentia pigmenti.

Other disorders

IKBKG gene variants can cause a condition known as X-linked susceptibility to mycobacterial disease. People with this condition have an increased risk of infection with forms of bacteria called mycobacteria. One type of mycobacterium causes tuberculosis, a respiratory disease that can be serious or life-threatening. Some mycobacterial infections are described as "opportunistic" because they do not cause illness in people with a normal immune system.

The *IKBKG* gene variants associated with X-linked susceptibility to mycobacterial disease change the structure of the IKBKG protein. The altered protein disrupts certain signaling pathways within immune cells. As a result, people with this condition often have fewer immune cells, or they may have immune system cells that function poorly. These cells cannot defend the body effectively against mycobacterial infections. Due to these immune issues, people with X-linked susceptibility to mycobacterial disease often require treatment to restore immune function in order to resist infection and keep inactive (latent) infections suppressed.

Because the *IKBKG* gene is on the X chromosome, which is one of the two sex chromosomes, individuals with one X chromosome (typical for males) who have a variant in their only copy of the gene can develop the condition. In people who have two X chromosomes (typical for females), a variant would have to occur in both copies of

the *IKBKG* gene to cause the disorder.

Other Names for This Gene

- FIP-3
- FIP3
- Fip3p
- IKK-gamma
- IP2
- NEMO
- NEMO_HUMAN
- NF-kappa-B essential modulator
- ZC2HC9

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of IKBKG (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=8517[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28IKBKG%5BTIAB%5D%29+OR+%28%28IKK-gamma%5BTIAB%5D%29+OR+%28NEMO%5BTIAB%5D%29+OR+%28NF-kappa-B+essential+modulator%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

- INHIBITOR OF NUCLEAR FACTOR KAPPA-B KINASE, REGULATORY SUBUNIT GAMMA; IKBKG (https://omim.org/entry/300248)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/8517)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=IKBKG[gene])

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Genomic Location

The *IKBKG* gene is found on the X chromosome (https://medlineplus.gov/genetics/chromosome/x/).

Last updated August 14, 2024