IKBKG Gene

Subjects: Genetics & Heredity
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Inhibitor of nuclear factor kappa B kinase subunit gamma

genes

1. Introduction

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 it is turned off (inactive), nuclear factor-kappa-B is attached (bound) to the IKK complex. In response to certain signals, the IKK complex turns on (activates) nuclear factor-kappa-B and releases it.

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 activates and releases nuclear factor-kappa-B. The activated factor then moves into the nucleus 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).

2. Health Conditions Related to Genetic Changes

2.1. Anhidrotic Ectodermal Dysplasia with Immune Deficiency

More than 20 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 reduced function of the immune system, resulting in recurrent infections, and abnormal development of ectodermal tissues. The *IKBKG* gene mutations 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 cells that form ectodermal tissues, resulting in immune deficiency and incomplete development of tissues of the ectoderm. The severity of the signs and symptoms of EDA-ID depends on the amount of protein function remaining; a greater level of protein function is associated with milder disease.

2.2. Incontinentia Pigmenti

More than 30 mutations in the *IKBKG* gene have been identified in people with incontinentia pigmenti, a condition characterized by skin, teeth, and nail abnormalities as well as vision loss and hair loss. The most common mutation, a complex rearrangement that deletes some genetic material from the *IKBKG* gene, accounts for more than 80 percent of all cases of the condition. This mutation probably leads to the production of an abnormally small, nonfunctional version of the IKBKG protein. Other people with incontinentia pigmenti have mutations that 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.

2.3. Osteopetrosis

Several mutations in the *IKBKG* gene have been found to cause a rare form of osteopetrosis with an X-linked pattern of inheritance. Researchers often refer to this condition as OL-EDA-ID, an acronym derived from each of the major features of the disorder. In addition to the abnormally dense bones characteristic of osteopetrosis, OL-EDA-ID is associated with abnormal swelling caused by a buildup of fluid (lymphedema) and anhidrotic ectodermal dysplasia, which affects the skin, hair, teeth, and sweat glands. Affected individuals also have immune deficiency, which allows severe, recurrent infections to develop.

The mutations responsible for OL-EDA-ID impair the normal function of the IKBKG protein, which reduces activation of nuclear factor-kappa-B. These changes disrupt certain signaling pathways within immune cells and cells that form ectodermal tissues, resulting in immunodeficiency and incomplete development of tissues of the ectoderm. It is unclear how *IKBKG* mutations lead to the other features of OL-EDA-ID, although the signs and symptoms are likely caused by abnormal nuclear factor-kappa-B signaling in other types of cells, including bone forming cells.

2.4. Other Disorders

IKBKG gene mutations also account for some cases of 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. Some of these foreign invaders are described as "opportunistic" organisms because they do not cause illness in people with a normal immune system. Another type of mycobacterium causes tuberculosis, a respiratory disease that can be serious or life-threatening. The *IKBKG* gene mutations responsible for X-linked susceptibility to mycobacterial disease alter the structure of the IKBKG protein. The defective protein disrupts certain signaling pathways within immune cells, which prevents the immune system from defending the body effectively against mycobacterial infection.

3. Other Names for This Gene

- FIP-3
- FIP3
- Fip3p
- IKK-gamma
- inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma
- IP2
- NEMO
- NEMO_HUMAN
- NF-kappa-B essential modulator
- ZC2HC9

References

1. Aradhya S, Woffendin H, Jakins T, Bardaro T, Esposito T, Smahi A, Shaw C, LevyM, Munnich A, D'Urso M, Lewis RA, Kenwrick S, Nelson DL. A recurrent deletion in the ubiquitously expressed NEMO (IKK-gamma) gene accounts for the vast majorityof incontinentia pigmenti mutations. Hum Mol Genet. 2001 Sep 15;10(19):2171-9.
2. Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti: a review and update on the molecular basis of pathophysiology. J Am Acad Dermatol. 2002Aug;47(2):169-87; quiz 188-90. Review.
3. Bruckner AL. Incontinentia pigmenti: a window to the role of NF-kappaBfunction. Semin Cutan Med Surg. 2004 Jun;23(2):116-24. Review.
4. Bustamante J, Picard C, Boisson-Dupuis S, Abel L, Casanova JL. Genetic lessonslearned from X-linked Mendelian susceptibility to mycobacterial diseases. Ann N YAcad Sci. 2011 Dec;1246:92-101. doi: 10.1111/j.1749-6632.2011.06273.x. Review.
5. Döffinger R, Smahi A, Bessia C, Geissmann F, Feinberg J, Durandy A, Bodemer C,Kenwrick S, Dupuis-Girod S, Blanche S, Wood P, Rabia SH, Headon DJ, Overbeek PA, Le Deist F, Holland SM, Belani K, Kumararatne DS, Fischer A, Shapiro R, ConleyME, Reimund E, Kalhoff H, Abinun M, Munnich A, Israël A, Courtois G, Casanova JL.X-linked anhidrotic ectodermal dysplasia with

immunodeficiency is caused byimpaired NF-kappaB signaling. Nat Genet. 2001 Mar;27(3):277-85.

6. Filipe-Santos O, Bustamante J, Haverkamp MH, Vinolo E, Ku CL, Puel A, FruchtDM, Christel K, von Bernuth H, Jouanguy E, Feinberg J, Durandy A, Senechal B,Chapgier A, Vogt G, de Beaucoudrey L, Fieschi C, Picard C, Garfa M, Chemli J,Bejaoui M, Tsolia MN, Kutukculer N, Plebani A, Notarangelo L, Bodemer C,Geissmann F, Israël A, Véron M, Knackstedt M, Barbouche R, Abel L, Magdorf K,Gendrel D, Agou F, Holland SM, Casanova JL. X-linked susceptibility tomycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12production. J Exp Med. 2006 Jul 10;203(7):1745-59.
7. Fusco F, Bardaro T, Fimiani G, Mercadante V, Miano MG, Falco G, Israël A,Courtois G, D'Urso M, Ursini MV. Molecular analysis of the genetic defect in alarge cohort of IP patients and identification of novel NEMO mutationsinterfering with NF-kappaB activation. Hum Mol Genet. 2004 Aug 15;13(16):1763-73.
8. Scheuerle AE, Ursini MV. Incontinentia Pigmenti. 1999 Jun 8 [updated 2017 Dec 21]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K,Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University ofWashington, Seattle; 1993-2020. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1472/
9. Shifera AS. The zinc finger domain of IKKγ (NEMO) protein in health anddisease. J Cell Mol Med. 2010 Oct;14(10):2404-14. doi:10.1111/j.1582-4934.2010.01054.x. Review.
10. Smahi A, Courtois G, Rabia SH, Döffinger R, Bodemer C, Munnich A, Casanova JL,Israël A. The NF-kappaB signalling pathway in human diseases: from incontinentia pigmenti to ectodermal dysplasias and immune-deficiency syndromes. Hum Mol Genet.2002 Oct 1;11(20):2371-5. Review.
11. Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A, Israël A,Heiss NS, Klauck SM, Kioschis P, Wiemann S, Poustka A, Esposito T, Bardaro T,Gianfrancesco F, Ciccodicola A, D'Urso M, Woffendin H, Jakins T, Donnai D,Stewart H, Kenwrick SJ, Aradhya S, Yamagata T, Levy M, Lewis RA, Nelson DL.Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause ofincontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium.Nature. 2000 May 25;405(6785):466-72.
12. Temmerman ST, Ma CA, Zhao Y, Keenan J, Aksentijevich I, Fessler M, Brown MR,Knutsen A, Shapiro R, Jain A. Defective nuclear IKKα function in patients withectodermal dysplasia with immune deficiency. J Clin Invest. 2012Jan;122(1):315-26. doi: 10.1172/JCI42534.
13. Uzel G. The range of defects associated with nuclear factor kappaB essentialmodulator. Curr Opin Allergy Clin Immunol. 2005 Dec;5(6):513-8. Review.
14. Verma UN, Yamamoto Y, Prajapati S, Gaynor RB. Nuclear role of I kappa BKinase-gamma/NF-kappa B essential modulator (IKK gamma/NEMO) in NF-kappaB-dependent gene expression. J

Biol Chem. 2004 Jan 30;279(5):3509-15.