NOD2 gene

nucleotide binding oligomerization domain containing 2

Normal Function

The *NOD2* gene (previously known as *CARD15*) provides instructions for making a protein that plays an important role in immune system function. The NOD2 protein is active in some types of immune system cells (including monocytes, macrophages, and dendritic cells), which help protect the body against foreign invaders such as bacteria and viruses. The protein is also active in several types of epithelial cells, including Paneth cells, which are found in the lining of the intestine. These cells help defend the intestinal wall against bacterial infection.

The NOD2 protein has several critical functions in defending the body against foreign invaders. The protein is involved in recognizing certain bacteria and stimulating the immune system to respond appropriately. When triggered by specific substances produced by bacteria, the NOD2 protein turns on (activates) a protein complex called nuclear factor-kappa-B. This protein complex regulates the activity of multiple genes, including genes that control immune responses and inflammatory reactions. An inflammatory reaction occurs when the immune system sends signaling molecules and white blood cells to a site of injury or disease to fight microbial invaders and facilitate tissue repair.

The NOD2 protein also appears to play a role in a process called autophagy, which cells use to surround and destroy bacteria, viruses, and other harmful substances. In addition to protecting cells from infection, autophagy is used to recycle worn-out cell parts and break down certain proteins when they are no longer needed. This process is also involved in the self-destruction of cells (apoptosis).

Health Conditions Related to Genetic Changes

Blau syndrome

At least 22 mutations in the *NOD2* gene have been found to cause Blau syndrome, an inflammatory disorder that begins in childhood and primarily affects the skin, joints, and eyes. These mutations change single protein building blocks (amino acids) in the NOD2 protein. All of these mutations result in a version of the NOD2 protein that is overactive, which can trigger an abnormal inflammatory reaction and cause swelling and irritation. However, it is unclear how the abnormally active protein causes the specific pattern of inflammation affecting the skin, joints, and eyes that is characteristic of Blau syndrome.

NOD2 gene mutations can also cause early-onset sarcoidosis, a similar condition that some researchers consider to be a noninherited version of Blau syndrome.

Crohn disease

Variations in the *NOD2* gene have been associated with an increased risk of Crohn disease, a complex disorder that causes inflammation of the digestive system. In particular, *NOD2* gene changes are associated with a form of Crohn disease that affects the lower part of the small intestine (the ileum) and the colon in populations of northern European descent. The three most common *NOD2* variations are found in about 40 percent of all people with Crohn disease. The most common of these, written as 3020insC or 1007fs, leads to the production of a NOD2 protein that is slightly shorter than normal. Other common variations change single amino acids in the NOD2 protein. It is unclear how these genetic changes increase the risk of developing Crohn disease. Studies suggest that changes in the *NOD2* gene prevent the protein from recognizing bacteria appropriately, allowing these microbes to grow unchecked and invade cells that line the intestine. An abnormal immune response to these bacteria may contribute to inflammation and the digestive problems characteristic of Crohn disease.

Yao syndrome

Several variations in the *NOD2* gene increase the risk of developing Yao syndrome, a disorder that causes episodes of fever and abnormal inflammation affecting many parts of the body. Most people with this condition have a variation in the *NOD2* gene written as IVS8+158, which is located in a region of the gene called intron 8. Another relatively common *NOD2* gene variation in people with Yao syndrome replaces the amino acid arginine with the amino acid tryptophan at position 702 in the NOD2 protein (written as Arg702Trp or R702W). These variations have also been identified in some people with Crohn disease (described above). About 20 percent of people with Yao syndrome have both the IVS8+158 and R702W variations, and some affected individuals have additional variations in the *NOD2* gene.

The effects of having one, two, or more variations in the *NOD2* gene is unclear, although studies suggest that these genetic changes may alter the activity (expression) of the *NOD2* gene. It is unknown how these variations might contribute to abnormal inflammation in people with Yao syndrome. Researchers suspect that environmental factors such as infections may also play a role in triggering the disease in people with genetic variants that increase their risk.

Cancers

A few studies have suggested a possible association between changes in the *NOD2* gene, particularly the common variation 3020insC (described above), and the development of several types of cancer. Although some of these studies found an increased risk of cancer in people with a *NOD2* gene variation, other research found no such association. It is unclear how changes in this gene might contribute to cancer risk.

Other disorders

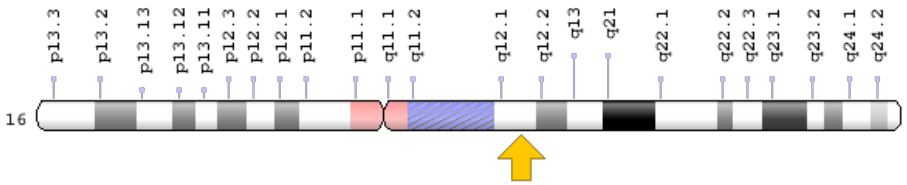
Several studies have considered variations in the *NOD2* gene as a possible risk factor for a condition called graft-versus-host disease (GVHD). GVHD can occur following certain cancer treatments, such as allogeneic stem cell transplantation. This procedure, which is typically used to treat cancers of the blood and immune system, replaces a patient's diseased blood-forming cells (a type of stem cell) with stem cells from a healthy donor. If the donor's stem cells (the graft) recognize the patient's body (the host) as foreign, they may attack organs and tissues such as the liver, digestive system, and skin. GVHD is the term used to describe this potentially severe reaction.

A few studies have suggested that variations in the *NOD2* gene influence the risk of developing severe complications of GVHD following an allogeneic stem cell transplant. The presence of *NOD2* gene variations in both the stem cell donor and the recipient is associated with the greatest risk of a severe reaction. However, other research has found no relationship between *NOD2* gene changes and the risk of developing GVHD.

Chromosomal Location

Cytogenetic Location: 16q12.1, which is the long (q) arm of chromosome 16 at position 12.1

Molecular Location: base pairs 50,693,587 to 50,733,077 on chromosome 16 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- ACUG
- BLAU
- CARD15
- caspase recruitment domain family, member 15
- caspase recruitment domain protein 15
- CD
- IBD1

- inflammatory bowel disease protein 1
- LRR-containing protein
- NOD2_HUMAN
- NOD2B
- nucleotide-binding oligomerization domain containing 2
- PSORAS1

Additional Information & Resources

Educational Resources

- Immunobiology: The Immune System in Health and Disease (fifth edition, 2001): The Front Line of Host Defense
  https://www.ncbi.nlm.nih.gov/books/NBK27105/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28CARD15%5BTIAB%5D%29+OR+%28NOD2%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+360+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN PROTEIN 2
  http://omim.org/entry/605956

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_NOD2.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=NOD2%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:5331
- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:64127
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/64127
- UniProt
  https://www.uniprot.org/uniprot/Q9HC29

Sources for This Summary

- Al Nabhani Z, Dietrich G, Hugot JP, Barreau F. Nod2: The intestinal gate keeper. PLoS Pathog. 2017 Mar 2;13(3):e1006177. doi: 10.1371/journal.ppat.1006177. eCollection 2017 Mar. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/28253332
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5333895/
- Elmaagacli AH, Koldehoff M, Hindahl H, Steckel NK, Trenschel R, Peceny R, Ottinger H, Rath PM, Ross RS, Roggendorf M, Grosse-Wilde H, Beelen DW. Mutations in innate immune system NOD2/CARD 15 and TLR-4 (Thr399Ile) genes influence the risk for severe acute graft-versus-host disease in patients who underwent an allogeneic transplantation. Transplantation. 2006 Jan 27; 81(2):247-54.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16436969
- Holler E, Rogler G, Herfarth H, Brenmoehl J, Wild PJ, Hahn J, Eissner G, Schölmerich J, Andreesen R. Both donor and recipient NOD2/CARD15 mutations associate with transplant-related mortality and GvHD following allogeneic stem cell transplantation. Blood. 2004 Aug 1;104(3): 889-94. Epub 2004 Apr 15.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15090455
- Hugot JP, Chamaillard M, Zouali H, Lesage S, Cézard JP, Belaiche J, Almer S, Tysk C, O'Morain CA, Gassull M, Binder V, Finkel Y, Cortot A, Modigliani R, Laurent-Puig P, Gower-Rousseau C, Macry J, Colombel JF, Sahbatou M, Thomas G. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature. 2001 May 31;411(6837):599-603.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11385576
- Kanazawa N, Okafuji I, Kambe N, Nishikomori R, Nakata-Hizume M, Nagai S, Fuji A, Yuasa T, Manki A, Sakurai Y, Nakajima M, Kobayashi H, Fujiwara I, Tsutsumi H, Utani A, Nishigori C, Heike T, Nakahata T, Miyachi Y. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome. Blood. 2005 Feb 1;105(3): 1195-7. Epub 2004 Sep 30.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15459013
- Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, Häfner R, Chamaillard M, Zouali H, Thomas G, Hugot JP. CARD15 mutations in Blau syndrome. Nat Genet. 2001 Sep;29(1): 19-20.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11528384
- Sidiq T, Yoshihama S, Downs I, Kobayashi KS. Nod2: A Critical Regulator of Ileal Microbiota and Crohn's Disease. Front Immunol. 2016 Sep 20;7:367. eCollection 2016. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/27703457
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5028879/
- Strober W, Watanabe T. NOD2, an intracellular innate immune sensor involved in host defense and Crohn's disease. Mucosal Immunol. 2011 Sep;4(5):484-95. doi: 10.1038/mi.2011.29. Epub 2011 Jul 13. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21750585
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3773501/
- Wang X, Kuivaniemi H, Bonavita G, Mutkus L, Mau U, Blau E, Inohara N, Nunez G, Tromp G, Williams CJ. CARD15 mutations in familial granulomatosis syndromes: a study of the original Blau syndrome kindred and other families with large-vessel arteritis and cranial neuropathy. Arthritis Rheum. 2002 Nov;46(11):3041-5.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12428248

- Yao Q, Shen M, McDonald C, Lacbawan F, Moran R, Shen B. NOD2-associated autoinflammatory disease: a large cohort study. Rheumatology (Oxford). 2015 Oct;54(10):1904-12. doi: 10.1093/rheumatology/kev207. Epub 2015 Jun 11.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26070941
- Yao Q, Zhou L, Cusumano P, Bose N, Piliang M, Jayakar B, Su LC, Shen B. A new category of autoinflammatory disease associated with NOD2 gene mutations. Arthritis Res Ther. 2011;13(5):R148. doi: 10.1186/ar3462. Epub 2011 Sep 14.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21914217
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3308076/
- Yao Q. Nucleotide-binding oligomerization domain containing 2: structure, function, and diseases. Semin Arthritis Rheum. 2013 Aug;43(1):125-30. doi: 10.1016/j.semarthrit.2012.12.005. Epub 2013 Jan 24. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23352252

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/NOD2

Reviewed: December 2017
Published: June 11, 2019

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services