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NOD2 Gene- A Review

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Abstract

Aim:

The aim of this study is to review NOD 2 gene in terms of its structure, its role in immunity, its mutations and interactions.

Background:

Nucleotide-Binding Oligomerisation Domain containing protein 2(NOD2 gene) is located in chromosome 16. It is an intracellular pattern recognition receptor. The vitamin D receptors signals through distal enhancers in the NOD2 gene, whose function was validated by chromatin immunoprecipitation and chromatin confirmation capture assays. This review helps in better understanding of NOD2 gene.

Reason:

NOD2 gene is found to be involved in the inflammatory diseases like crohn's disease, osteosarcoma and in innate immunity of a individual. Hence, a thorough understanding of its structure and function is essntial to increase immunity and cure diseases involving NOD2 gene.

INTRODUCTION:

NOD2 gene is a intracytoplasmic member belonging to a family known as NLR proteins(1-4). It is present in the long arm of chromosome 16 at position 21,mostly in human cells which are responsible for immunity like monocytes, macrophages, dentritic cells and is also found in the epithelial cells lining the intestine. This gene plays an important role in the innate immunity, autophagy in their normal form and if it is abnormal or absent may pave way for diseases like Crohn disease, Blau syndrome etc. The other names of this gene being BLAU, CARD15, CD, IBD1, PSORAS1, caspase recruitment domain family member 15, inflammatory bowel disease protein 1, nucleotide binding oligomerisation domain containing 2.

FUNCTION:

This gene is mainly used for our body's immunity, protecting our body from invading microorganisms like bacteria and viruses. NOD2 gene when stimulated by a bacteria it creates certain responses such that the body destroys the pathogen. Activated NOD2 gene now activates a protein named nuclear factor kappa-B. This gene controls the activity of multiple genes that contain immunological and inflammatory reactions. First an inflammatory reaction followed by an immunological reaction wherein the immune cells reach the injured area and destroys the invading pathogen. Furthermore this gene is also responsible for self destruction of certain unwanted proteins and cells which are no more needed to the organism. This process is called autophagy.

ROLE OF NOD2 GENE IN CROHN'S DISEASE:

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tracts. The exact cause of this disease is unknown but it is suspected to be hereditary. This disease proceeds by the immune system thinking the commensals which are present in the intestines as pathogens and provokes an immune response. It is known to be caused when there is deficiency in the NOD2 gene. This was found out by the study which was done by Watanabe et al in 2004 where the IL-12p70 synthesis were increased in the antigen presenting cells in NOD2 deficient mice and the IL-12p70 synthesis being decreased in a mice with normal NOD2 produced mice(5). NOD2 gene has 2 N terminals of caspase activation recruitment domains and some C terminals called leucine rich repeats (6).This activates the NFkB signalling pathway. Mutated variant 1007fs will have a truncated protein lacking part of leucine rich repeats which is not effective in inducing LPS mediated NFkB activation(7).From 2001, there have been many studies of that stated NOD2/CARD15 gene as a responsible factor in the development of Crohn's disease. (7-12). The most important variant of NOD2 gene said to be responsible for the initiation of the disease is 1007fs, R702W, G908R(8-11).Inoue et al in his study reported the lack of common NOD2 variants in Japanese people with Crohn's disease(13). Hugot et al and Ogura et al, showed in their study a link between CARD15 variants and Crohn's disease(7,8).Inoue et al also suggested that there may be other disease that may cause variations in NOD 2 gene. Louis et al. In his study found the behavior and location of the disease for 25 years and concluded that the behavior of Crohn's disease differed excessively but the location of the gene was stable(14). In recent times, for certain complex diseases, mapping variants are now performed in a isolated populations where evaluated for(15,16,17,18).The alleles with frequency of 1% in a rapidly growing population was simulated to mate randomly using computer technology and after 20 generations the most common allele's frequency was 6% whereas some alleles were lost(15). Both glucocorticoids and mineralocorticoids both effectively inhibit NFkB. There are certain antimicrobial peptides called defensins. They are small cationic arginine peptides with a molecular weight of 3.5kDa(19,20). Several investigations indicate that defensins are differently expressed in Crohn's disease and ulcerative colitis(21,22,23)

ROLE OF NOD2 GENE IN BLAU SYNDROME:

Blau syndrome is a autosomal dominant disorder of the early childhood which includes granulomatous dermatitis, synovism and uveitis. however other organs are also tend to be involved and show symptoms like cranial neuropathies (24), fever (25,26,27,28), cerebral infarction(29), malignant

hypertension(25,26,27)and renal lesions(30). Hence the Blau syndrome entity is more confusing and more complex than expected previously and are suspected as a subset of familial granulomatous syndrome(31). The susceptibility locus for this disease is the chromosome 16p12-21(32) .A study was done by Wang et al where a linkage mapping was performed for 10 families wherein 5 families had mutation in NOD2 gene. This result showed there is a mild chance for NOD 2 gene to be responsible for blau syndrome. Another study done by Miceli-Richard et al showed a result of 2 variants of NOD2 gene in the families affected with Blau syndrome(33). NOD2 gene is said to be found in monocytes which play a role in granulomas seen in Blau syndrome patients(34).

CONCLUSION:

Studies have also shown that NOD2 variants have been involved in several complications in graft versus host reaction. The presence of NOD2 gene variant in both donor and recipient had an added risk. Further studies also hint the action of NOD2 gene in the etiology and development of cancer. Studies also revealed an increased risk of cancer in patients with a NOD2 variant. So, a better understanding of the gene and its action may help in the treatment of certain diseases by modifying its action with the help of the science and technology.

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