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Miscellaneous

Nucleotide-binding oligomerization domain containing 2: Structure, function, and diseases

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ABSTRACT

Objectives: To systematically review literature about the structure and function of nucleotide-binding oligomerization domain containing 2 (NOD2) and its disease association.
Methods: The English literature was searched using keywords "NOD2" and "disease". Relevant original and review articles were reviewed.
Results: NOD2 is an intracellular protein and shares similar molecular structure with NOD1, pyrin, and cryopyrin. There are more than 100 NOD2 gene mutations, some of which have been linked to diseases such as Crohn disease, Blau syndrome, and NOD2-associated autoinflammatory disease (NAID). The NOD2 variants located in the leucine-rich repeat (LRR) region are susceptible to Crohn disease, and the variants in the nucleotide-binding domain (NBD) and in between the NBD and LRR are associated with Blau syndrome and NAID, respectively. No disease association with the gene variants has been found in rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, psoriasis/psoriatic arthritis, adult sarcoidosis, granulomatous polyangiitis, or multiple sclerosis. The potential association of the NOD2 variants with graft-versus-host-disease remains controversial. NOD2 functions mainly through RICK or RIP2 to activate p38 mitogen-activated protein kinases and NF-κB, resulting in inflammatory response, and enhanced autophagic activity. Biologic therapy may be beneficial for NOD2-associated diseases, and new drug development may be realized based upon the signaling pathways.
Conclusions: NOD2 gene mutations are associated with several diseases, and some of the mutations are of diagnostic value in Blau disease and NAID. To understand the NOD2 function, disease association, and its pathogenesis is important given the ever increasing clinical significance of NOD2.

Nucleotide-binding oligomerization domain containing 2 (NOD2) is a member of a family of intracellular proteins with N-terminal caspase recruitment domains (CARDs), which was first discovered by Nunez's group in 2001 [1]. Also known as caspase recruitment domain-containing protein 15 (CARD15), NOD2 was recently renamed as nucleotide-binding oligomerization domain (NOD)-like receptor with a CARD (NLRC2) [2]. Since the first report of an association of the NOD2 variants with Crohn disease by Hugot et al. [3], extensive studies have been focused on a potential association of NOD2 with other diseases as well. Given few review articles available to cover the current knowledge and advance of NOD2 association with diseases, this review concentrates on the NOD2 structure, function, and its disease association, and it is also structured for the ease of use for all levels of readership, clinicians in particular.

Methods

PubMed was used for the literature search between 2001 and September 2012. The systematic search was limited to publications in English since 2001, when NOD2 was first reported, and the following keywords were used: "NOD2" or "NOD2 and disease". The computerized search was completed with a manual search of pertinent reference lists from the relevant articles retrieved. Abstracts of congresses were excluded. A PRISMA

Abbreviations: CARD, caspase recruitment domain; CARD15, caspase recruitment domain 15; DM, diabetes mellitus; EGFR, epidermal growth factor receptor; FMF, familial Mediterranean fever; GPA, granulomatous polyangiitis; GVHD, graft-versus-host disease; IBD, inflammatory bowel disease; IPF, idiopathic pulmonary fibrosis; LRR, leucin-rich repeat; MAP, mitogen-activated protein; MDP, muramyl dipeptide; MS, multiple sclerosis; NACHT, central NOD-like receptor; NAID, NOD2-associated autoinflammatory disease; NBD, nucleotide-binding domain; ND, not significant; NF-κB, nuclear factor-κB; NLRC2, nucleotide-binding oligomerization domain (NOD)-like receptor with a CARD; NOD1, nucleotide-binding oligomerization domain 1; NOD2, nucleotide-binding oligomerization domain 2; PGN, peptidoglycan; RA, rheumatoid arthritis; RICK, rip-like interacting caspase-like apoptosis-regulatory protein kinase; RIP2, receptor-interacting serine/threonine-protein kinase 2; SLE, systemic lupus erythematosus; TLR, toll-like receptor; TNFα, tumor necrosis factor α

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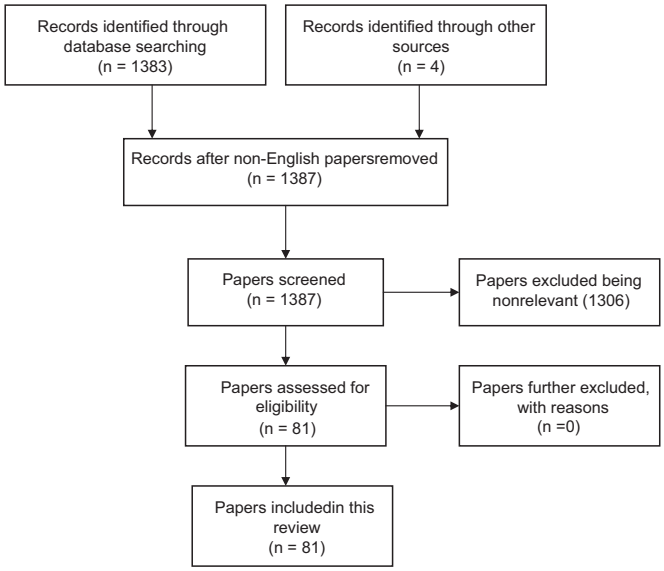

Fig. 1. PRISMA flowchart to depict the data search from literature.

statement details the data-gathering process (Fig. 1) [4]. A narrative biomedical review methodology was employed in this paper [5].

Results

NOD2 gene and protein structure

The NOD2 gene has been mapped to chromosome 16q12-21 [1], and the NOD2 gene mutations are schematically represented (Fig. 2A). Some of the gene mutations are also called variants or polymorphisms [6]. There are 118 NOD2 gene variants reported to date (〈http://www.fmf.igh.cnrs.fr/ISSAID/infevers/search.php?n=6〉); these gene mutations are named according to the DNA sequence and protein variants and carry usual names. For example, the gene mutations with the usual names of R702W (SNP8), G908R (SNP12), and 1007fs (SNP13) are also designated as Arg702Trp, Gly908Arg, and leu1007profs, respectively, on the basis of protein variants. There are 12 exons in the NOD2 gene, with the mutations G908R and 1007fs in exons 8 and 11, respectively, in the LRR region, R702W, R703C in exon 4, and IVS8+158 in between the NBD and LRR, and many other gene mutations in the NBD of exon 4 [7].

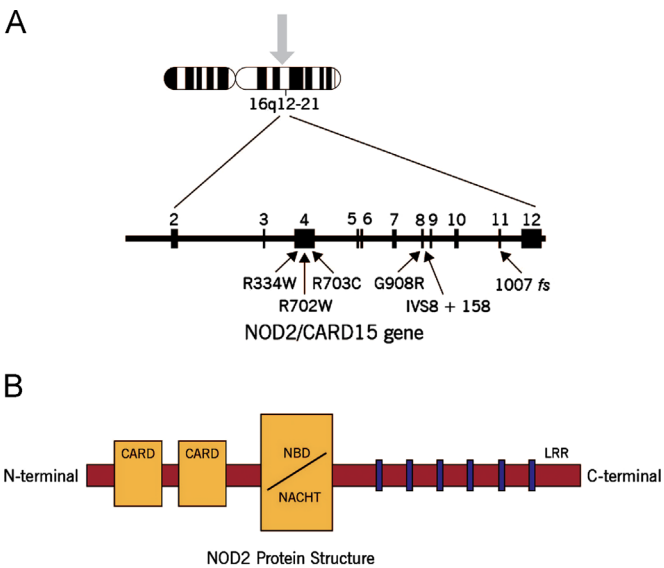

Fig. 2. Schematic representation of the NOD2 gene and protein structures. The NOD2 gene mutations are categorically located: LRRs (1007fs and G908R), NBD (R334Q, R334W, etc.), and in between LRRs and NBD (R702W, R703C, and INS8+158) (A). The NOD2 protein comprises 3 domains: 6 LRRs, NBD, and 2 CARDs (B).

The protein of NOD2 comprises 1040 amino acids, containing 2 N-terminal CARDs, a central NOD-like receptor (NACHT) or NBD, and 6 C-terminal LRRs (Fig. 2B) [8]. The NOD2 protein is primarily present in the cytosols of monocytes, macrophages, dendritic cells, and the intestinal endothelium [9]; the NOD2 protein structure is similar to that of NOD1, pyrin, and cryopyrin, but there are differences. NOD1 has 9 LRRs and 1 CARD. Pyrin linked to familial Mediterranean fever (FMF) and cryopyrin to cryopyrin-associated periodic fever disease have a pyrin domain (PYD) in addition to the LRR and central NACHT [10].

NOD2 and diseases

The disease association with the NOD2 variants has been extensively studied in numerous disorders [11]. In addition to the involvement of the NOD2 in bacterial and viral infections, the NOD2 variants are linked to the following diseases.

The NOD2 gene mutations have been extensively studied in inflammatory bowel disease (IBD), and the 3 common variants 1007fs, G908R, and R702W are susceptible to Crohn disease rather than ulcerative colitis [12]. The respective frequency of the 3 variants in IBD and healthy controls is summarized in Table 1 based upon a large study of a European population [12].

NOD2 gene mutations have been also associated with pediatric Blau syndrome, which is characterized by the triad of granulomatous dermatitis, polyarthritis, and uveitis [13]. The NOD2 variants identified in Blau syndrome are mainly in the NBD of the NOD2 rather than the LRR region [14].

We have reported a new autoinflammatory disease associated with NOD2 mutations [15], which is designated as NOD2-associated autoinflammatory disease (NAID) [16]. This disorder is characterized by periodic fever, dermatitis, polyarthritis, gastrointestinal symptoms, and sicca-like symptoms, and is currently associated with the NOD2 variants IVS8+158, R702W [16], and R703C [17]. These variants are located in between the NBD and LRR regions of the NOD2.

Numerous studies of the NOD2 gene mutations in several other rheumatic diseases have failed to demonstrate an association between the 3 common variants and the rheumatic diseases (Table 2). Concerning the potential association between psoriasis/psoriatic arthritis and the NOD2 variants, most studies did not support the presence of the association. Only 1 study reported an association between psoriatic arthritis and R702W. Nonetheless, a

Table 1
The Frequency of the 3 Common NOD2 Gene Mutations in IBD and Normal Population.

Population	1007fs Cases/*n* (%)	G908R Cases/*n* (%)	R702W Cases/*n* (%)	References
European				
Crohn	96/906 (11)	55/906 (6)	98/906 (11)	[12]
UC	4/318 (2)	1/318 (0.3)	10/318 (3)	
Healthy	4/206 (2)	2/206 (1)	9/206 (4)	
Country				
England	22/587 (1.9)	13/587 (1.1)	49/587 (4.2)	[53]
America	21/273 (3.8)	9/273 (1.6)	20/273 (3.7)	
Canada	6/100 (3.0)	4/100 (2.0)	10/100 (5.0)	

Crohn, Crohn disease; UC, ulcerative colitis.