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TOPIC HIGHLIGHT

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NOD2: Ethnic and geographic differences

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Abstract

Investigations into the inheritance of the three risk alleles R702W, G908R and 1007fsInsC in NOD2 associated with susceptibility to Crohn's disease have demonstrated a remarkable amount of heterogeneity across ethnicities and populations, with regional variation across Europe for example, suggesting local founder effects. In non-Caucasian populations Crohn's disease continues to increase in incidence but this increase appears not to be a consequence of variation in NOD2, further advancing the accumulating evidence for other susceptibility loci. Frequencies of the known alleles are compared across populations in health and disease and evidence for additional alleles in NOD2 is reviewed. Based on its position on chromosome 16 coincident with some other autoimmune disease susceptibility localizations, research has targeted NOD2 variation as the potential cause of other autoimmune disorders. While these investigations have mostly returned negative findings, two diseases, Blau Syndrome and Graft versus Host Disease, have been shown to be caused by risk alleles in NOD2. As is frequent in complex disease investigations, some results await validation, but the identification of NOD2 and the differences within and across population raises intriguing questions about the population genetics of the variation at this locus.

Key words: NOD2; Crohn's disease; Inflammatory bowel disease; Ethnicities

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NOD2 AND CROHN'S DISEASE

NOD2 (also known as CARD15) was the first gene underlying susceptibility to Crohn's Disease (CD) to be identified with three common mutations being described[1,2] and an analysis of the haplotypes carrying the three major mutations suggests that these represent three independent mutation events[3]. Two of the mutations lead to amino acid substitutions (R702W) and (G908R), while the third (L1007fs) is a single base insertion that results in a stop codon that truncates the protein. In addition, a growing number of "private" mutations that are unique to individual pedigrees have been described but supporting evidence for causality based on functional evidence is rarely reported for these rare alleles[4,5]. The majority of mutations in CARD15 that are associated with CD occur in the Leucine Rich Repeat domain-the part of the protein believed to be involved in intracellular sensing of bacterial components[4].

Each of these mutations is more properly called a "risk allele" (RA) because possessing one or more of the alleles confers an increased risk on an individual, but does not mean that disease will necessarily develop. The argument about whether the three risk alleles confer loss or gain of function remains unresolved but it is clear that the normal function of NOD2 is as a receptor for bacterially derived molecules known as pathogen associated molecular pattern (PAMP) molecules in the intestine. Our understanding of the disease processes and the link between innate and adaptive immune responses has advanced remarkably because of the identification of NOD2 in up to 50% of CD. Nevertheless carriage of risk alleles is neither necessary nor sufficient for disease.

One prediction that comes from our understanding of complex disease is that such risk alleles will occur in the healthy population albeit at lower frequencies than in disease. Allele frequencies of the three RAs in CD have been reported for many populations and are summarized in Table 1. As predicted, there is a significant elevation of the allele frequencies in CD in comparison to that in healthy controls in most populations. Since few studies report on additional mutational assessment of NOD2 in their populations, it is not possible to assess whether unique or population specific mutations exist. In a number of cases a stronger association has been reported in pediatric cohorts[5]. This result has been borne out by multivariate analysis of CD that indicates that early age of onset is significantly associated with carriage of NOD2

Table 1 Allele frequencies for the NOD2 RAs in different ethnic groups

Ethnicity /population	Frequency (patient/control) R702W	Frequency (patient/control) G908R	Frequency (patient/control) L1007fs	Other features	Reference
Greek	0.1 (0.01)	0.14 (0.03)	0.18 (0.06)	EAO	[22]
Hungary	0.16 (0.08) over all 3 mutations				[23]
Israeli Arabs	0.04 (0.01) over all 3 mutations				[12]
Israeli Jewish	0.05	0.18	0.08	pediatric	[24]
Israeli Jewish	0.06	0.11	0.06	adult	[24]
USA Jewish	0.03 (0.05)	0.09 (0.03)	0.07 (0.02)		[6]
USA Caucasian	0.06 (0.05)	0.06 (0.01)	0.13 (0.02)	EAO	[5]
USA Hispanic	0 (0.03)	0 (0.01)	0.02 (0.004)	EAO	[5]
USA African American	0.08 (0.02)	0.0 (0)	0.008 (0.04)	EAO	[5]
Australia	0.11 (0.05)	0.02 (0.10)	0.07 (0.01)		[25]
New Zealand	0.03 (0.02)	0.07 (0.05)	0.08 (0.008)		[26]
South Africa coloured	0.06 (0.03)	ND (0.005)	0.01 (0.04)		[14]
Han Chinese	0 (0)	0 (0)	0 (0)		[13]

risk alleles. This enrichment is likely to be a consequence of the stronger genetic contribution to disease observed in many predominantly inherited diseases when cohorts with an early age of onset are studied. In fact the improvement in linkage and or association evidence observed in regions identified by genome wide scans when cohorts are conditioned on carriage of NOD2 may be a consequence of the effective selection for early age of onset rather than evidence for epistasis with NOD2.

Researchers in the International IBD Genetics Consortium have compared the frequency and impact of NOD2 RAs in disease groups from fourteen centers from Europe, North America and Australia (Cavanaugh *et al* in preparation) and have found a strong association between early age of onset and the NOD2 RAs, particularly for the L1007fs allele in those families. They have also noted that the P268S allele is also strongly associated with disease, but since functional assays do not support the rare variant in disease causation it is unlikely that this allele is itself disease associated[6]. Thus this variant is likely to be in linkage with other causative allele (s) whether in NOD2 itself or at some distance from the coding region. In the search for regulatory mutations the 5' region of NOD2 has been studied but have no disease associated alleles (Schreiber pers com). Nevertheless, the recent description of remote Conserved Non-Coding regions (CNCs)[7] that are implicated in disease gene expression suggests that variation that is quite distant from NOD2 may regulate its expression and potentially impact in disease.

GEOGRAPHIC AND ETHNIC DIFFERENCES

Several authors have commented on evidence for a North-South gradient in CD in Europe with a higher frequency of disease in northern Europe than southern Europe[8]. This hypothesis is extremely intriguing given the similarities already identified between multiple sclerosis and inflammatory bowel disease. Nevertheless, the frequencies of NOD2 risk alleles do not appear to underlie this gradient. Vind *et al*[9] compared Danish and Portuguese patients and controls and found no evidence to support a North - South gradient in allele frequencies. Arnott *et al*[10] have reported that NOD2 RAs are at lower frequencies in Scottish, Irish and Scandinavian CD than in England, central Europe or North America and went on to argue that these data demonstrating regional heterogeneity across Europe are suggestive of regional founder events with respect to NOD2 risk alleles. For example, allele frequencies and Population Attributable Risk (PAR) reported for NOD2 RAs in Finland are similarly low yet the incidence of disease is relatively high[11]. These data highlight the existence of other contributing susceptibility loci in CD.

Studies in disease populations from central and southern Europe confirm a consistent pattern of association between NOD2 RAs and CD (Table 1)[10]. In North America admixture probably accounts for the low frequency of NOD2 RAs in African Americans and Hispanics[5]. Bonen *et al*[6] reported a significantly higher frequency of the G908R allele in Ashkenazi jews than in non-jewish whites and that association has been conformed in other studies[12]. At the same time the frameshift mutation that is well represented in most ethnicities is at lower frequencies in Ashkenazi Jews. With the exception of Greece and Ashkenazi Jews, the G908R allele is rarely elevated in frequency disease in most disease groups (Table 1).

In a comparison of NOD2 allele frequencies in 3575 Caucasian healthy individuals from sixteen different centers from Europe, North America and Australia, Hugot et al (in preparation) described significant heterogeneity between centers with Australia and Finland having the lowest frequencies of known variants while Belgium and Canada has the highest. Those authors also note that the frequency of the RAs is highest in central and southern Europe, in good agreement with other studies.

Analyses of non-Caucasian groups has failed to identify a significant contribution from the known NOD2 RAs. In South-East Asian populations that have been studied to date, NOD2 RAs are absent from Japanese and Korean populations (reviewed in Arnott *et al* 2004) and more recently, are also absent in Han Chinese[13]. Little information is available for South American or African populations with the exception of a recent report of low

NOD2 allele frequencies in coloured South Africans of Indian descent[14]. CD in Indians is more prevalent than in Chinese or Malays and the incidence and the prevalence of inflammatory bowel diseases appears to be increasing in Asian countries though this trend is more evident for ulcerative colitis than CD[15].

The pattern that emerges from these studies both of disease groups and healthy controls suggests that CD occurs at quite variable rates across geographical regions and that in some populations where NOD2 RA carriage rates are at a high, those alleles are present in up to 50% of individuals with CD. Nevertheless the incidence of CD in populations with substantial carriage of RA eg Belgium and Canada is remarkably similar to those with lower rates, suggesting that CD occurs in those groups because of other genetic susceptibilities, raising the issue of differential genotype by environmental interaction. ie the specific agents that initiate disease process in one population may be different to those in other populations depending on the underlying genetic susceptibility. This suggests that different micro-organisms may initiate disease in different populations depending on the underlying genetic susceptibilities of that population. Such a scenario may lead to the heterogeneity, both genotypic and phenotypic, observed in inflammatory bowel disease generally. These issues will only be resolved as further research identifies other IBD susceptibility loci and functional analyses identify the microorganisms that likely underlie disease initiation.

ASSOCIATION WITH OTHER DISEASES

Interestingly, two other diseases have been associated with NOD2 mutations. The first non IBD association was with a rare disease long known to map to the pericentromeric region of chromosome 16 that has also been shown to carry mutations in NOD2 that result in the simple Mendelian inheritance of Blau syndrome[16]. Mutations that confer susceptibility to Blau syndrome occur in the nuclear binding domain (NBD) of the protein, which is believed to be independent of LRR interactions. The second association has been shown with gastrointestinal Graft versus Host disease[17]. In this case, disease course is exacerbated in the recipient if either donor or host carries any of the three risk alleles associated with CD. This increased susceptibility to rejection is probably a function of altered epithelial reactivity in the ileum leading to an impaired microbial response. Recently there has been a suggestion that NOD2 RAs may be involved in breast cancer in the individuals with first degree relatives with lung cancer[18] however this study requires validation.

OTHER AUTOIMMUNE DISEASES

In addition a number of inherited autoimmune diseases have been shown to demonstrate linkage to the pericentromeric region of chromosome 16 that houses NOD2, including rheumatoid arthritis and lupus erythematosus. As a consequence of the observation that autoimmune disease appear to cluster in specific regions of the genome[19] and might therefore share some common underlying genetic susceptibilities, a number of researchers have tested their different disease groups for the common mutations in NOD2. Diseases in which association with known NOD2 mutations have been investigated are shown in Table 2 along with evidence for linkage evidence to chromosome 16 and ethnicity of patient (and control if reported). The small subset of patients with spondyloarthropathy with chronic gut inflammation show association with NOD2 RAs and share many features with CD[20]. Those authors commented that this group of patients is likely to progress to fulminant CD. The closely related phenotypes of atopic eczema, asthma and allergic rhinoconjunctivitis[21] have been shown to have an association with NOD2 variants, although the causative alleles were not identified. With these exceptions, these studies have failed to demonstrate a fundamental association of autoimmune diseases with NOD2, nevertheless the central role that the described NOD2 RAs have in CD remains unequivocal.

Table 2 Results of association analysis between NOD2 RAs and other inherited diseases

Disease	Linkage to chromosome 16	Ethnicity	Association	Reference
Allergy and atopy	yes	German	yes[1]	[21]
Behcet's disease	yes	UK, Turkish and Arab	no[2]	[27]
Breast cancer with lung cancer FDR[3]	no	Poland	yes	[18]
Idiopathic pulmonary fibrosis	unknown	Italian	no	[28]
Necrotising enteritis	unknown	France	no[4]	[29]
Psioratic arthritis	yes	Newfoundland	yes	[30]
Psioratic arthriris	yes	UK	no	[31]
Rheumatoid arthritis	no	USA	no[5]	[32]
Sarcoidosis	no	Danes	no	[33]
Sarcoidosis	no	United Kingdom	no	[34]
Spondyloarthropathy with chronic gut inflammation	no	Belgium	yes	[20]
Systemic lupus erythematosus	yes	Spain	no	[35]
Type 1 diabetes	yes	Scandinavia	no	[36]
Wegener's granulomatosis	no	North America	no	[37]

[1]Both disease and protective associated haplotypes are described; [2]Direct sequencing to identify polymorphisms failed to identify association by case-control; [3]FDR first degree relative. The association reported occurs only in breast cancer patients who have a first degree relative with lung cancer but not in individuals without; [4]All exons and exon/intron boundaries of NOD2 were sequenced; [5]Genoyped for 3 common and a further 12 SNPs in NOD2 with no haplotype association observed.

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