Opening the flood gates? Association of NOD2 with Crohn's disease

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It's been a long time coming, but now two papers report a clear cut identification by linkage mapping of a gene involved in a common human disorder — Crohn's disease (CD). Importantly, they also indicate how the innate immune system might be involved in the aetiology of CD, because the identified gene — *NOD2* — encodes an intracellular receptor for bacterial lipopolysaccharides (LPS) that activates NFκB, a target of the innate immune signalling pathway and a transcriptional regulator of inflammatory genes.

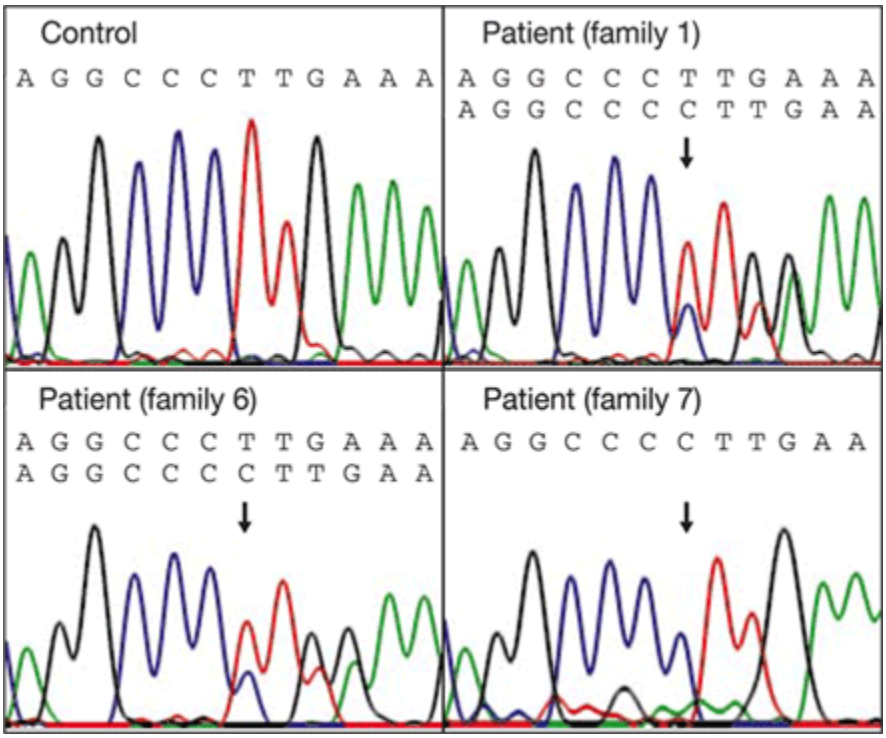
CD is a chronic inflammatory gut disorder, thought to be caused by an abnormal inflammatory response to enteric microbes. In 1996, a CD susceptibility locus, *IBD1*, was identified on chromosome 16. Little progress has been made since, but it is this locus that the two research teams — one European, the other US-based — tackled in their studies, using positional-cloning and candidate-gene strategies, respectively.

Hugot *et al.* took a decisive step when they identified association of CD to an allele of a chromosome-16 microsatellite marker. Despite the borderline significance of this association, the authors went on to identify putative transcripts in the region of this marker, and identified over 30 single nucleotide polymorphisms (SNPs) by sequencing the region from affected and unaffected individuals. Several turned out to be non-synonymous variants in a chromosome — 16 gene, *NOD2*. Three of these SNPs — each independently associated with disease susceptibility — altered the leucine-rich repeat (LRR) region of NOD2, which is required for LPS recognition.

Having previously identified *NOD2*, Ogura *et al.* considered it a candidate for CD because of its chromosome-16 location. On sequencing the gene from CD individuals, they identified an insertion that caused two frameshift mutations in the LRR region and the premature truncation of NOD2. In *in vitro* assays, this mutant NOD2 produced considerably diminished levels of NFκB activation in response to bacterial LPS compared to wild-type NOD2.

So how could *NOD2* contribute to susceptibility to CD? The innate immune system regulates the immediate immune response to bacterial pathogens, components of which are recognized in host immune cells by specific receptors, such as NOD2. A defect in this recognition might lead to an exaggerated inflammatory reaction being mediated by the adaptive immune system. Alternatively, NOD2 might act to trigger cytokines that dampen inflammatory responses. Although NOD2 does not account for all susceptibility to CD, it does provide a first glimpse into the aetiology of the disease and should speed the discovery of other CD loci and future therapies, and improve its diagnosis. These papers are hopefully the first of many such successes in grappling with the genetic basis of multifactorial, common disease.

Story by Jane Alfred, *Nature Reviews Genetics* [http://www.nature.com/nrg/]



DNA sequence electropherograms of the *NOD2* gene A portion of *NOD2* exon 11 DNA sequence from control and three CD-affected individuals. The control sequence codes for full-length NOD2 protein. The patients from families 1 and 6 are heterozygous for a cytosine insertion at position 3020 in the *NOD2* gene. The wild-type sequence in these panels is in the upper position and is read GCC-CTT-GAA. The sequence containing the cytosine insert is in the lower position and is read GCC-CCT-TGA. The extra cytosine base (marked by the arrows) causes a framshift mutation to occur, and the TGA sequence immediately downstream is recognized as a stop codon, causing the NOD2 protein to be truncated. The patient from family 7 is homozygous for the same cytosine insertion.

Important Links

Live PubMed searches

(1) NOD2

(2) IBD1

(3) REVIEWS

Additional NCBI resources

NOD2 in LocusLink

IBD1 in LocusLink

Genes and Disease [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=gnd.section.116]

Medline Plus [http://www.nlm.nih.gov/medlineplus/crohnsdisease.html]

Box: Search the genome for the *NOD2* gene polymorphisms

Click on the link below to start an html tutorial.

Are there additional polymorphisms in the *NOD2* gene? [http://www.ncbi.nlm.nih.gov/Coffeebreak/CB21_Crohns/mapv1.html]