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Genomewide Association Study of Leprosy

TO THE EDITOR: Zhang and colleagues (Dec. 31 issue)1 report that genes in the nucleotide-binding oligomerization domain containing 2 (NOD2)—mediated signaling pathway are associated with susceptibility to infection with *Mycobacterium leprae* in China. India has the world’s greatest leprosy disease burden. We therefore genotyped the single-nucleotide polymorphisms (SNPs) that were implicated by Zhang and colleagues in two Indian case–control cohorts (492 patients in New Delhi and 382 in Kolkata).2,3 We also genotyped 273 cases and 221 controls from Mali, West Africa.4 We observed associations between disease and SNPs at C13orf31 (the gene encoding chromosome 13 open reading frame 31) (rs3764147, *P* = 6.1×10⁻⁸) and CCDC122 (the gene encoding coiled-coil domain containing 122) (rs9533634, *P* = 1.1×10⁻⁵) (Table 1); both genes were of unknown function. We did not, however, observe associations between disease and the other four non–major histocompatibility complex (MHC) genes related to the NOD2 pathway (*NOD2*, *RIPK2*, [the gene encoding leucine-rich repeat kinase 2]), *TNFSF15* (the gene encoding tumor necrosis factor (ligand) superfamily member 15), and *LRRK2* (the gene encoding leucine-rich repeat kinase 2)) (Table 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org), despite reasonable power to detect the effect sizes observed by Zhang et al.4 An analysis of 27 additional SNPs at NOD2 in the New Delhi cohort provided support for the absence of a consistent association at this locus (Table 2 in the Supplementary Appendix). These results indicate heterogeneity among populations and suggest that future functional studies should focus on populations in which the relevant genetic association may occur. Nevertheless, a robust association of the Crohn’s disease chromosome 13q14.11 locus5 containing C13orf31 and CCDC122 with leprosy in China, India, and Mali provides support for a molecular link between mycobacterial infection and Crohn’s disease.

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Table 1. Associations with Leprosy for Replicated Single-Nucleotide Polymorphisms on Chromosome 13q14.11, According to Case–Control Population.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Original Study</th>
<th>Present Study</th>
<th>New Delhi</th>
<th>Kolkata</th>
<th>Mali</th>
<th>Combined Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3764147</td>
<td>C13orf31</td>
<td>1.68 (1.57–1.80)</td>
<td>1.59 (1.34–1.89)</td>
<td>2.7×10⁻³</td>
<td>6.4×10⁻²</td>
<td>1.1×10⁻⁵</td>
<td>6.1×10⁻⁸</td>
</tr>
<tr>
<td>rs9533634</td>
<td>CCDC122</td>
<td>0.76 (0.70–0.82)</td>
<td>0.70 (0.59–0.82)</td>
<td>1.5×10⁻³</td>
<td>3.6×10⁻¹</td>
<td>1.1×10⁻⁵</td>
<td>1.1×10⁻⁵</td>
</tr>
</tbody>
</table>

*C13orf31* denotes the gene encoding chromosome 13 open reading frame 31, CCDC122 the gene encoding coiled-coil domain containing 122, CI confidence interval, and SNP single-nucleotide polymorphism.

TO THE EDITOR: In a genomewide association study, Zhang and colleagues identified the NOD2 pathway associated with susceptibility to leprosy. Their findings were consistent with those of studies showing the role of NOD2 in the recognition of mycobacteria. However, NOD2 interacts with toll-like receptors (TLRs) during recognition of mycobacteria, and polymorphisms in either TLR2 or TLR4 have been shown to influence susceptibility to leprosy. Therefore, it may seem surprising that no signal of association was detected between TLRs and leprosy in the study by Zhang et al. The accompanying editorial posits that a subgroup “of Crohn’s disease cases may have a mycobacterial cause.” A candidate culpable organism causes Johne’s disease in ruminants, an affliction evocative of Crohn’s disease. Interspecies comparisons may be illuminating. Cattle with the NOD2 defect are three times as likely to contract Johne’s disease as cattle with wild-type NOD2 in the same herd.

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Dr. Greenstein reports submitting patent applications based on the inhibition of mycobacteria including the M. avium subspecies paratuberculosis by medications used to treat Crohn’s disease. No other potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: A similar proinflammatory immune response has been observed in paucibacillary leprosy and in the contained form of Crohn’s disease. In contrast, such an immune response has not been detected in the more aggressive, multibacillary form of leprosy and in the more aggressive form of Crohn’s disease. These findings are now mirrored in an intriguing commonality between human genetic defects in multibacillary leprosy and Crohn’s disease reported on by Zhang et al. The accompanying editorial posits that a subgroup “of Crohn’s disease cases may have a mycobacterial cause.” A candidate culpable organism causes Johne’s disease in ruminants, an affliction evocative of Crohn’s disease. Interspecies comparisons may be illuminating.

Cattle with the NOD2 defect are three times as likely to contract Johne’s disease as cattle with wild-type NOD2 in the same herd.

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The Authors Reply: Using three case-control samples from India and West Africa, Wong et al. undertook a follow-up study of our recently identified leprosy susceptibility SNPs and confirmed the strong associations of C13orf31 and CDCCI22, highlighting the commonality of leprosy susceptibility loci among diverse populations. Although they did not detect the associations in the other
Barrett's Esophagus

TO THE EDITOR: Sharma (Dec. 24 issue) says that ablation is not recommended for nondysplastic Barrett's esophagus because of an unacceptably high number of patients who would need to be treated (the number needed to treat) to prevent one case of adenocarcinoma. The estimate of 250 as the number needed to treat is artificially high, however. The number needed to treat is 1 divided by the absolute risk reduction. In the meta-analysis by Wani et al., the incidence of adenocarcinoma in patients with untreated nondysplastic Barrett's esophagus was 0.6% per patient-year of follow-up, as compared with 0.16% in patients treated with ablation. The absolute risk reduction is therefore 0.6%−0.16%, or 0.44% per patient-year of follow-up. The studies in this meta-analysis varied in the length of follow-up, but all follow-ups were multiple years in length. Assuming a follow-up of just 5 years, the number needed to treat would be 45, not 250. Other studies of ablation for nondysplastic Barrett's esophagus also show a much lower number needed to treat — approximately 23 rather than 250.

Sharma's estimate of the number needed to treat limits ablation to prevention of adenocarcinoma only; however, ablation also prevents the development of high-grade dysplasia and subsequent progression to cancer. For the inclusion of the aggregate end points of high-grade dysplasia and cancer, the number needed to treat would be lower still.

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Dr. Ganz reports being a coinventor of the Halo system of radiofrequency ablation and having equity in and serving on the board of directors of the manufacturing company, BARRX Medical. No other potential conflict of interest relevant to this letter was reported.