Finding inflammatory bowel disease genes will not lead to a cure

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The contribution of genetic factors to the pathogenesis of inflammatory bowel disease (IBD) is limited. The concordance between monozygotic twins is only 5% to 14% for ulcerative colitis, which suggests that environmental factors play a major role in the pathogenesis of the disease. On the other hand, for Crohn's disease (CD), the concordance may be as high as 50% (1,2). However, this overestimates genetic contribution because twins not only share genes but also a common childhood environment. Indeed, significant clustering among siblings with IBD suggests that birth order influences sibling phenotype and that the early environment is important (3).

The identification of the nucleotide oligomerization domain 2/caspase recruitment domain *15* (*NOD2/CARD15)* gene marked a major advance in our understanding of mechanisms underlying CD (4,5). However, the association between *NOD2/CARD15* and CD phenotype is far from straightforward. In one published knock-out model (6), *NOD2* mutation impaired mucosal immune response and increased susceptibility to infection. Conversely, a knock-in model that introduced a *NOD2* mutation similar to the human variant, increased nuclear factor-kappa B activation and enhanced mucosal inflammatory responses to bacterial peptidoglycan in experimental colitis (7). However, no matter what its effect, the *NOD2/CARD15* allele is carried by less than 50% of patients with CD and up to 20% healthy North Americans and Europeans (8). Hence, it is neither necessary nor sufficient to cause the disorder.

Temporal trends in epidemiology provide the most striking and compelling evidence of environmental influence on the pathogenesis of CD. CD was a relatively rare disorder over 100 years ago, but its incidence rose abruptly and dramatically in the middle third of the 20th century, and may now have reached a plateau (9). Such abrupt changes in epidemiology can only result from changes in the environment, which suggest that the role played by genetic factors is modest and largely permissive. Similarly, ethnic differences in the incidence of CD do not appear to reflect genetic predisposition and are lost with migration and/or changes in lifestyle (10,11). Despite their ancestry, children of migrants assume the CD incidence of their new environment.

CD appears to be strongly associated with domestic hygiene, urbanization, affluence and westernization. Geographical trends suggest that CD is more common in northern climates, but this gradient is often confounded by socioeconomic status (9). CD has also been attributed to the altered gut immune response that results from reduced helminth exposure and colonization (12). Observed behaviours that influence the incidence of CD include smoking, use of oral contraceptives, high sugar and high fat diets, breastfeeding and use of toothpastes (9,13). Conversely, appendectomy and smoking protect against ulcerative colitis (9).

Early childhood exposures may be the most important determinants of future CD. Associations between the birth month and the incidence of CD suggest that changes in climate or seasonal pathogens may be important contributing factors (14,15). The major paradigm underlying proposed childhood risk factors is the so-called hygiene hypothesis, that associates CD with improved domestic cleanliness and reduced early antigen exposure (16,17). Although early studies (18-20) were confounded by recall bias, acute childhood gastroenteritis (perhaps in the context of limited prior antigen exposure) appears to increase the risk of CD; the incidence of CD is inversely associated with infant mortality (11,21). Access to hot water and use of separate bathrooms have all been identified as risk factors (16,17). A particularly intriguing hypothesis links CD to the advent of refrigeration and increased exposure to psychrotrophic microorganisms (22).

The most intimate interaction between humans and their environment is the juxtaposition of intestinal mucosa and gut luminal contents. Overwhelming evidence suggest that gut flora play a pivotal role in inducing and maintaining the inflammation of CD. Colitis in the murine interleukin-10 knock-out model requires gut flora, and can be attenuated by introducing specific probiotics or antibiotic treatment (23-26). Despite several compelling hypotheses, efforts to link specific pathogens to CD have not been successful. However, human CD may be associated with shifts in mucosal flora (27) and its course may be altered by antibiotic treatment (28). The use of probiotics for the treatment of CD is now a focus of intense clinical research.

In summary, IBD is a complex, polygenic disorder with incomplete genetic penetrance and poor genotype-phenotype correlation. Ultimately, the genetic contribution to the pathogenesis of IBD may be largely permissive. There is overwhelming evidence that environmental exposure drives disease expression and natural history. Indeed, there has been an abrupt and dramatic change in the epidemiology of CD over the past 100 years that can only reflect shifts in behaviour, lifestyle and environment. Only a better understanding of early environmental triggers will allow us to prevent and cure IBD in the future. Genetics may tell us where to look for a cure, but it is environmental research that will tell us what to do.

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