IBS

Genetic susceptibility to postinfectious IBS

Genetic risk factors related to epithelial integrity of the intestinal barrier and innate immune responses are predictors of postinfectious IBS, report Villani *et al.* from Canada. Their report is the first descriptive study to assess potential genetic factors involved in susceptibility to postinfectious IBS.

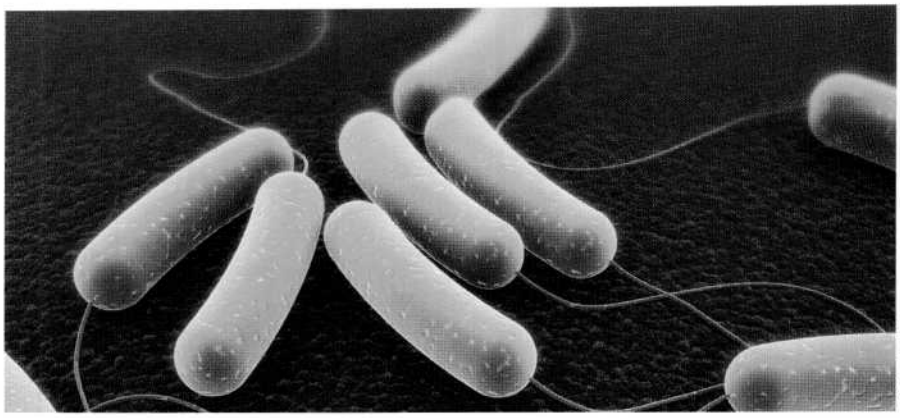
The research was based on data gathered from individuals who were residents of Walkerton, Canada, after an outbreak of acute bacterial gastroenteritis in May 2000. The outbreak originated from contamination of the municipal water supply by livestock fecal residue and led to >2,300 residents becoming ill with bacterial gastroenteritis (from pathogens including *Escherichia coli* and *Campylobacter jejuni*), 27 cases of hemolytic urine syndrome and 7 deaths.

John Marshall, lead author of the study, explains that "the outbreak was an awful human tragedy, but also an opportunity to learn more about the phenomenon of postinfectious IBS and its causes."

The Walkerton Health Study was started in 2002 to study the epidemiological data and long-term health outcomes of individuals who were residents of Walkerton at the time of the outbreak. The study includes 4,315 residents of whom 1,253 fulfilled the criteria for Villani and colleagues' postinfectious IBS genetic study.

Previous work showed that >36.2% of residents who were exposed to gastroenteritis during the outbreak had IBS when assessed by use of the Rome I criteria 2–3 years afterwards. Furthermore, IBS in the Walkerton population was found to be associated with increased intestinal permeability.

"Intestinal epitheilial integrity, defects in innate immune response and changes in serotonin secretion and metabolism could all have a role in postinfectious IBS," explains Marshall. Accordingly, the authors conducted a genetic study by use of a candidate gene approach to assess potential genetic risk factors for postinfectious IBS that were related to these specific pathways. The aim of the study was to identify gene polymorphisms that confer susceptibility or protection to postinfectious IBS.



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The study included four groups of individuals: controls who did not experience acute gastroenteritis during the outbreak and didn't develop IBS; individuals who self-reported acute gastroenteritis and subsequent IBS; individuals who developed acute gastroenteritis but not subsequent IBS; and individuals who experienced acute gastroenterititis and subsequent IBS.

51 candidate genes previously characterized and potentially associated with IBS, serotoninergic pathways, or the innate immune reponse were identified. Of these genes, 71 genetic polymorphisms were selected for analysis and the univariate association between genetic variants and postinfectious IBS was assessed by use of mixed effects logistic regression models.

The analysis identified genetic risk factors of postinfectious IBS related to epithelial integrity and the innate immune response. Four genetic variants were associated with postinfectious IBS, including two variants located in *TLR9*, which encodes a pattern recognition receptor, one variant located in *CDH1*, which encodes a tight junction protein, and one variant located in *IL6*, which encodes a cytokine. These associations did not withstand corrections for multiple testing, but fine mapping of *TLR9*, *CDH1* and *IL6* revealed that these variants were indeed independent risk factors for postinfectious IBS. "Of note, these genotypes remained independent predictors of postinfectious IBS even when controlled for known clinical risk factors," says Marshall. "Overall, these findings support a model for IBS pathogenesis that relates changes in gut flora to disturbances in gut permeability and the initiation and maintenance of a submucosal immune response."

Both clinical and genetic risk factors seem to contribute independently to postinfectious IBS. Villani and colleagues hope to replicate these findings in another cohort, but acknowledge the difficulty of finding another cohort of a similar size to the Walkerton Health Study. "Ultimately, we hope to develop a predictive model that integrates genetic, clinical and microbial factors to identify individuals at high risk of postinfectious IBS after dysentery. This could help clinicians to provide an accurate prognosis, but also target novel therapies that might attenuate or prevent long-term sequelae of enteric infection," explains Marshall.

Rachel Jones

Original article Villani, A.-C. *et al.* Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. *Gastroenterology* **138**, 1502–1513 (2010)

IN BRIEF

IBD

Either a combination of infliximab plus azathioprine or infliximab monotherapy is more likely than azathioprine monotherapy to result in corticosteroid-free clinical remission in patients with moderate to severe Crohn's disease, a randomized double-blind trial has found. The investigators randomly allocated 508 adults who had not had prior immunosuppressive or biologic therapy to receive either combination therapy or monotherapy. Combination therapy achieved the best results, with 56.8% of patients in corticosteroid-free clinical remission after 26 weeks of treatment, compared with 44.4% receiving only infliximab and 30.0% receiving only azathioprine.

Original article Colombel, J. F. *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N. Engl. J. Med.* **362**, 1383–1395 (2010)

GENETICS

13 new regions have been identified that contain variants linked with celiac disease in a second-generation genome-wide association study. 4,533 patients with celiac disease and 10,750 control individuals were genotyped. Most of the loci identified include genes whose products have immune functions, and four have key roles in thymic T-cell selection.

Original article Dubois, P. C. A. *et al.* Multiple common variants for celiac disease influencing immune gene expression. *Nat. Genet.* **42**, 295–302 (2010)

CANCER

In 731 samples of colorectal cancer (CRC) taken from participants in two prospective cohort studies, 142 samples (19%) showed overexpression of the hypoxia-inducible factor 1α gene (*HIF1α*). This characteristic was associated with poor prognosis. The researchers suggest that HIF1A protein overexpression could be used as a prognostic biomarker in patients with CRC.

Original article Baba, Y. *et al.* HIF1A overexpression is associated with poor prognosis in a cohort of 731 colorectal cancers. *Am. J. Pathol.* **176**, 2292–2301 (2010)

OBESITY

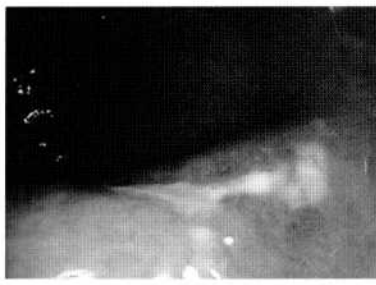
Several biological and social factors are associated with rapid weight gain in early childhood, according to the results of a UK national cohort study. The researchers prospectively assessed 11,653 preschool children for weight gain between the ages of 3 and 5 years, and examined the contribution of 26 known risk factors. A child was likely to gain weight if their parents were overweight, their mother had smoked during pregnancy, or if they were an only child. The researchers suggest that obesity prevention programs before and during pregnancy and during a child's early years should focus on parental weight status and smoking habits, as these are modifiable risk factors.

Original article Griffiths, L. J. *et al.* Risk factors for rapid weight gain in preschool children: findings from a UK-wide prospective study. *Int. J. Obes.* **34**, 624–632 (2010)

IBD

Occult inflammation causes IBS symptoms in patients with IBD

IBS-type symptoms in patients with IBD are probably caused by occult inflammation and are not the result of true IBS, according to the findings of a new study by Fergus Shanahan and colleagues from University College Cork in Ireland.



The familiar appearance of aphthous ulceration at colonoscopy, confirming unsuspected active Crohn's disease in a patient thought to be in remission but complaining of IBS-type symptoms. Colonoscopy was prompted by the finding of elevated fecal calprotectin levels. Courtesy of F. Shanahan.

IBS-type symptoms are commonly reported in patients with IBD and the prevalence of both diseases in the general population means that it is statistically possible for patients with IBD to have IBS. However, proving that IBS and IBD coexist is problematic because the two diagnoses are mutually exclusive. Even in patients who have IBD that is in remission it is difficult to evaluate IBS-type symptoms—it is not possible to be sure that the disease really is in remission and that no inflammation is present without performing exhaustive and invasive tests.

"To approach this [problem]," explains Shanahan, "we selected patients with IBD who were considered by their physician to be in remission by conventional clinical criteria and who fulfilled predefined criteria of remission." 106 patients (62 with Crohn's disease and 44 with ulcerative colitis) were recruited. The authors then assessed the prevalence of IBS-type symptoms and used a non-invasive test—the measurement of fecal calprotectin levels—to look for evidence of occult gastrointestinal inflammation.

"The study confirmed that IBS-type symptoms are common in patients with IBD, even those who are thought to be in clinical remission," reports Shanahan. Indeed, almost 60% of patients with Crohn's disease and 40% of patients with ulcerative colitis had symptoms that fulfilled Rome II criteria for IBS.

Shanahan goes on, "The most important finding was that when we looked at fecal calprotectin we found that the highest levels of calprotectin were in the patients with IBS-type symptoms compared with healthy controls and those patients without IBS-type symptoms."

This finding means that the IBS-type symptoms reported in patients with IBD that is thought to be in remission actually reflect ongoing IBD activity. If gastrointestinal symptoms in these patients are inappropriately attributed to IBS instead of occult inflammation then anti-inflammatory treatment may be delayed and the risk of complications enhanced.

So, what do the findings of this study mean for clinical practice? "The main implication of the work is that symptomatic patients [with IBD] should always be evaluated for treatable inflammation," says Shanahan. "IBD is IBD unless proven otherwise." Basic and clinical investigators are now working together to study the relationship between minimal or occult inflammation and the genesis of symptoms.

Natalie J. Wood

Original article Keohane, J. *et al.* Irritable bowel syndrome in patients with inflammatory bowel disease: a real association or reflection of occult inflammation? *Am. J. Gastroenterol.* doi:10.1038/ajg.2010.156