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 epithelial 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

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these specific pathways. The aim of the study was to identify gene polymorphisms that confer susceptibility or protection to postinfectious IBS.

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 gastroenteritis and subsequent IBS.

51 candidate genes previously characterized and potentially associated with IBS, serotonergic pathways, or the innate immune response 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.

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