ROLE OF SEROLOGIC AND GENETIC TESTING IN IBD
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The roles for serologic and genetic testing in IBD as of 2012 continue to evolve although their clinical utility has been relatively limited aside from the use of pharmacogenomics related to thiopurines. However, there are a number of potential utilities that continue to evolve and include: insights into etiopathogenesis; diagnosis of IBD and differentiation between different phenotypes, and; prognostic classification.

The identification of, now, over one hundred genes associated with IBD provide etiopathogenic targets, however, this has yet to translate into clinical utility.1 The association between NOD2/CARD15 and stenosing ileal disease has been well-established but has not been incorporated into clinical algorithms.2 Other genes offer clues to pathogenesis that are currently being evaluated in animal models.3

The primary role for genetic testing in IBD has been related to pharmacogenomics and, in particular related to the genetic polymorphisms of thiopurine methyltransferase (TPMT) that impact on the metabolism of thiopurines1 as genotypes do correlate with functional TPMT activity. However, most U.S. clinicians utilize functional TPMT testing rather than genetic testing when initiating thiopurine therapy to minimize toxicity for patients with low or intermediate functional activity that are at risk of bone marrow suppression when dosing is initiated on a mg/kg basis.

In contrast to genetics, serologic testing offers a number of clinical and translational potentials beyond the role of pathogenesis.4 IBD-associated antibodies and their presumed targets have recently been reviewed5 and include the well-studied peri-nuclear antinuclear cytoplasmic antibodies (pANCA), antibodies to the carbohydrate epitopes cell wall of Saccharomyces cervisiae (ASCA) and other carbohydrate cell wall epitopes (anti-glycans), antibodies to the outer membrane transport protein of E. coli (OmpC), antibodies to Pseudomonas-associated sequence I2, antibodies to bacterial flagellin (CBir1), antigoblet cell antibodies, antibodies to tropomycin microfilament protein, and pancreatic autoantibodies that are increased in patients with IBD compared to healthy controls. From the standpoint of diagnosis, most gastroenterologists will provide endoscopic (and histopathologic sampling) means of classification for patients with a suspicion of IBD; whereas, pediatricians may prefer to start a diagnostic work-up with serologic testing that, if negative, offers reasonable assurance that a child does not have IBD. However, the ability of these assays to differentiate UC from CD is insufficiently sensitive or specific to offer clinical utility beyond the capabilities of endoscopy and histology that remain a gold standard for the diagnosis of UC and CD and indeterminate colitis; keeping in mind that the indeterminate (or even UC) phenotype may not be stable (in particular after a colectomy and ileoanal anastomosis).6 In general, I consider pANCA a marker for colonic disease and ASCA, anti-glycans and other bacterial antibodies as markers of small bowel disease. Hence, it is not surprising that a group of patients with left colonic (UC-like) features have positive pANCA serologies.7

Serologies may have a greater role in predicting the course of disease than in diagnoses. Indeed, one of the most intriguing examples comes from populations where the presence of positive anti-glycan serologies predicts the development of IBD in asymptomatic individuals.8 While patterns of serologic markers tend to stay stable over time9 there may be differences in patterns depending upon age at diagnosis.10 There is scant data on changes after surgical procedures such as resections in Crohn’s disease or colectomies in UC. High titers of pANCA have long been known to be associated with more refractory UC11 and there have been numerous studies demonstrating that the greater number and titers of serologies are predictive of a more complicated (strictures, fistulas, surgeries) course of Crohn’s disease.12-15 Most recently, Lichtenstein et al. have demonstrated how a combination of serologic and genetic markers can be used to predict a complicated disease course.16 However, most of the patients presented with the complications at the same time as serologic testing such that prospective studies are necessary to determine whether serologies can be used to predict subsequent complications for patients presenting with non-stricturing, non-fistulizing Crohn’s disease. Since NOD2/CARD15 mutations correlate with stricturing ileal Crohn’s disease, a phenotype that frequently requires surgical resection; it will be important and relevant to identify independent predictors separate from those identifying ileal stricturing diseases.

Hence, at the present time serologies and genetic studies are being utilized from a translational and basic research standpoint to evaluate pathogenetic mechanisms. In clinical practice there has yet to be a defined role for genetic testing in either suspected or confirmed cases of IBD. Serologies may identify a group of patients/relatives at risk of developing IBD but the absence of interventions and the undefined predictive value undermine the utility of testing families. At present, endoscopy and histology remain the gold standard...
for discriminating between UC and CD although the presence of ASCA, anti-glycans, and anti-bacterial protein serologies are more predictive of (small bowel) Crohn’s disease. As far as predictors of disease course are concerned, most patients present with clinical features that are predictive of the course although multiple serologies and high serologic titers also correlate with more complex disease behaviors.

REFERENCES