

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Genotype/Phenotype Correlations in Inflammatory Bowel Disease

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G&H Can you describe the historic evolution of phenotypic classification for inflammatory bowel disease?

LH Over the years, different groups have worked to develop classification systems for Crohn's disease (CD) and ulcerative colitis (UC). One of the first widely recognized classification systems was developed by the International Working Party in Rome, which convened in 1991. At that time, anatomic distribution, surgical history, and clinical behavior of the disease (as characterized by inflammation, fistulization, or stenosis) were established as the main parameters in determining disease phenotype. In 1998, the World Congress of Gastroenterology met in Vienna and updated the classification system by including age of onset (before or after 40 years of age), along with disease location and behavior.

The most recent working party to examine phenotypic classification came together in Montreal in 2005. The group made some important changes to the earlier Vienna system, based on our current knowledge of the disease. The group redefined the age-of-diagnosis classification, recognizing early onset of disease to include three categories: patients diagnosed at age 16 and under, those diagnosed from the ages of 17 to 40, and those diagnosed after the age of 40. The group also recognized a limitation of the Vienna classification scheme, in that the Vienna system categorized disease locations as mutually exclusive. Patients with colonic disease could not be acknowledged as also having upper gastrointestinal (GI) tract involvement.

This was changed in the Montreal classification system. In addition, under the Vienna system, perianal disease was considered synonymous with fistulizing disease. In the Montreal system, it was established that perianal disease was not sufficient for a classification of fistulizing disease, and perianal disease was designated as a disease-behavior modifier. This evolution in phenotyping provides a useful background for different centers and groups to work with as they move forward in their studies.

G&H How can phenotyping be related to ongoing research of genetic markers for inflammatory bowel disease?

LH One of the major challenges in inflammatory bowel disease (IBD) research and treatment is that, taken as a whole, IBD is a very heterogeneous disorder with a wide variety of manifestations. Over the years, several IBD susceptibility genes have been identified. As these genes have been discovered, the question has arisen as to whether they can be linked to specific disease patterns or phenotypes, which could aid in predicting disease outcome and thus treatment course.

From the other direction, defining study participants with a specific phenotype creates a more homogenous population within the group of patients with IBD and can enhance our ability to find a new genetic mutation. The researchers who recently identified the interleukin (IL)-23 receptor gene looked at patients with ileal disease only, which allowed them to work with a more homogenous population. They performed a genome-wide association study and identified the IL-23 receptor allele as a predictor

of disease susceptibility, which shows how phenotyping patients can assist in a genetic study.

G&H Are measures of disease severity incorporated into phenotyping systems?

LH The concept of disease severity is difficult to incorporate into phenotypic classifications because, in IBD patients, disease location and disease behavior are dynamic. When classifying patients for studies, particularly genetic studies, phenotype is determined at a specific time point. Typically, disease behavior is surveyed retrospectively, and patients are not necessarily labeled with a specific level of disease severity. In phenotyping schema, classifications of disease behavior provide a measure of severity, but in most of the studies that have been published to date, disease duration has not been factored, so the progressive needs for steroid therapy or surgery, which generally define level of severity, cannot be measured across a study population.

G&H At this point, how uniform is the phenotypic classification system that is used among researchers and clinicians?

LH Various institutions and consortia classify patients with their own systems, which may or may not be based on the recommendations of the international working party classification systems. This creates another challenge with regard to the generalizability of genetic studies and studies utilizing phenotyping systems. However, I believe investigators are recognizing the importance of a more uniform phenotyping system for our patients. For example, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) IBD Genetics Consortium recently reported the results of a study they performed demonstrating the reliability and validity of their phenotyping system which is similar to the Montreal Working Party classification system. This demonstrated the importance of uniformity in phenotyping patients across centers.

G&H How do you foresee genotype/phenotype relations ultimately affecting the use and indications of medical therapies?

LH In the near future, we will be able to identify different genetic and serologic markers that predict disease course. If we can predict disease course, we will be better able to tailor individual therapies to particular patients. Further, we can better understand disease behavior if we phenotype patients longitudinally.

If we can identify patterns of disease and different markers that will predict how the disease will behave, we may be able to use less aggressive medications with fewer

side effects in patients we know will have a more indolent disease course. Therapies that may be more effective overall but are associated with a higher rate of side effects can be reserved for patients we believe will have a more disabling course. Reliable, consistent phenotypic classification plays an important role in this process because we need to understand, again, that CD is not just one disease. It is a heterogeneous disease with many different patterns that respond differently to therapy.

G&H Do you think that established phenotyping will affect future clinical trial design?

LH I think that, to an extent, phenotyping already does affect clinical trials. Subgroup analyses of large trials essentially look at phenotype to see what types of patients respond better to different therapies. In the future, we will continue with this practice and, as a result, uniform phenotyping will help us to apply clinical trial findings in general practice.

G&H Do clinicians need to change their standard diagnostic practices in order to firmly and consistently establish phenotype in new patients?

LH In order to establish phenotype, a clinician must assess the extent and nature of a patient's disease. Historically, this has best been done utilizing radiologic and endoscopic studies. Our ability to assess the extent and nature of disease has improved with the introduction of newer modalities such as the wireless capsule endoscopy procedure. Thus, when a new patient is diagnosed, it is important to perform a thorough assessment of their GI tract to understand the extent of disease and better determine phenotype.

Phenotype classifications are largely perceived in the community as a research tool, but I believe they can be useful to clinicians as well, particularly as we gain a better understanding of how genetic markers and serologic markers can assist us in caring for our patients.

G&H Is administration of capsule endoscopy feasible as standard practice in all new patients?

LH Physicians need to assess individual patients and make that determination based on the circumstances of the case. In patients with complications such as bowel stricture, capsule endoscopy should obviously not be prescribed. Other radiologic tests, including small bowel follow-through and computed tomography (CT) enterography also provide valuable information about the small bowel. Another issue practitioners need to consider is the cost of these examinations. For example, in UC patients

with simple proctitis or others where there is no question regarding their classification, there may be no need for these newer modalities such as capsule endoscopy. However, from a research standpoint, there is considerable interest in capsule endoscopy to examine whether there is disease involvement in areas that may have been missed previously.

G&H Do serology panels provide a less costly alternative to capsule endoscopy?

LH Serology panels serve a different purpose from capsule endoscopy. It is important to have objective evidence of the extent and nature of disease, through the standard endoscopic, histologic, and radiologic tests. Currently marketed IBD serology panels can be helpful in screening patients for IBD or helping to determine IBD type in unclassified disease. They are not sensitive enough to be used alone for these purposes. Some of the markers have been associated with small bowel disease and particular disease behavior. Nonetheless, at this time these markers do not replace standard diagnostic modalities.

G&H Is there currently a place for genetic testing in clinical practice?

LH At this time, the only IBD susceptibility gene that has very strong evidence to support a genotype/phenotype association is *NOD2/CARD15*. CD patients with the *NOD2/CARD15* genetic mutation are more likely to

have ileal disease, complicated disease, and also to have an earlier age of disease onset. Although other IBD susceptibility genes have been confirmed, genotype/phenotype correlations have not been as well replicated for them. Thus, at this time, genotype testing and genotype/phenotype relations are not clinically useful. However, as our research advances and more associations are made, perhaps there will be a place for genetic testing in clinical practice some day.

Suggested Reading

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