MEETING SUMMARY

2015 James W. Freston Single Topic Conference: A Renaissance in the Understanding and Management of Irritable Bowel Syndrome

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In honor of one of its past presidents, the American Gastroenterological Association (AGA) started the James W. Freston Single Topic Conference, which has been held annually since 2009. The 2015 Freston conference included state-of-the art lectures and posters on current scientific insights in irritable bowel syndrome (IBS; Supplementary Tables 1 and 2), and was organized on behalf of the American Neurogastroenterology and Motility Society and the Neurogastroenterology and Motility section of the AGA. Although the meeting content spanned a wide range of topics, this summary focuses on the scientific advances concerning the prevalence, symptoms, risk factors, biomarkers, and pathophysiology involving brain–gut interactions.

Prevalence and Symptoms

IBS has a global prevalence of 1 in 10 adults[1] and fluctuating symptom patterns of abdominal pain, disturbed defecation, and extraintestinal symptoms. IBS represents a significant health burden owing to direct medical costs and indirect costs. Costs in the United States per patient per year have been estimated to range from $742 to $7547. Men are more likely to report IBS with diarrhea (IBS-D) and women are more likely to report IBS with constipation. Sociocultural factors can influence prevalence, health care–seeking behavior, symptoms, and treatment response.

The worldwide prevalence of pediatric IBS is 13.5%; childhood functional abdominal pain disorders including IBS increase the risk for adult functional gastrointestinal disorder (FGIDs). Thus, approximately 40% of children with functional abdominal pain will become adults with either IBS or another FGID and 40% will continue to suffer from an anxiety disorder into adulthood.

IBS is a heterogeneous and multidimensional disorder. The underlying physiologic and psychological determinants of symptoms vary and, without an understanding of these determinants, treatment can be nonspecific and varies in its success. An updated classification system for IBS, the Rome IV diagnostic criteria, along with a multidimensional clinical disease profile to aid in clinical management will be released in May 2016.

Risk Factors

Genetics

A heritable component of IBS is supported by family and twin studies and a Swedish proband study. To date, there have been limited findings in candidate gene studies; one of the fundamental flaws has been the need for $\geq$2000 patients to achieve the p values of 10^{-7} typically required in genetic association studies. One exception is *TNFSF15* gene, which is associated with risk of IBS in several European and US cohorts.[2] The first genome-wide association study of IBS in 5466 individuals from a Swedish population-based (twin) cohort, identified 1 locus at 7p22.1, which includes the genes *KDELR2* (KDEL endoplasmic reticulum protein retention receptor 2) and *GRID2IP* (glutamate receptor, ionotropic, delta 2 [Grid2] interacting protein), which showed consistent IBS risk effects.[3] This finding was replicated in 6 case-control cohorts from Europe and the United States. Currently, a collaborative project is examining genetics of IBS in >30,000 European population-based cohorts, and in well-characterized IBS patients and controls from Europe and the United States.

Abbreviations used in this paper: **AGA, American Gastroenterological Association; BA, bile acid; EALs, early adverse life events; FGID, functional gastrointestinal disorder; IBS, irritable bowel syndrome; IBS-D, IBS with diarrhea; SCFA, short chain fact acid; TRPV, transient receptor potential vanilloid.**

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The feasibility of identifying genetic variants by risk allele frequency and strength of genetic effects is shown in Figure 1. IBS may be caused by a number of relatively common alleles, each of which increases the risk of disease by a small percentage. However, there are also limitations of exome DNA sequencing alone, for example, failure to appraise epigenetics or tissue protein expressions resulting from the genes. Progress in genetic association studies relies heavily on accurate phenotyping, which currently depends primarily on symptoms. The imprecision of a symptom-based diagnosis may have contributed to slow progress in genetic studies. Some advances in genetics and pharmacogenetics have resulted from the use of endophenotypes, such as colonic transit measurements or brain signatures.

Combined Genetics and Expression

The heterogeneity and complexity of IBS requires use of multiple types of –omics approaches (eg, whole exome/genome sequencing, transcriptomics, proteomics, metabolomics, epigenomics, brain connectome, etc) that allow assessment of various mechanistic networks. Thus, it is important to characterize the IBS phenotype using standardized symptom measures in conjunction with historical information about environmental exposures, early life stress, and medical history to capture potential epigenetic influences, and to obtain other quantitative variables such as diet, physiologic measurements, and microbiome.

Advances in bioinformatics will facilitate the creation of the databases needed to understand complex intracellular and intercellular networks, linkage analyses, and association analyses needed to find the missing heritability component of IBS.[4] Using these data and new integrated analytic platforms, it is anticipated that pathways and networks may unmask the pathogenesis of IBS and ultimately lead to a paradigm shift toward systems medicine.[5] The field of IBS is just starting to exploit genome-wide association studies, exome DNA sequencing, RNA sequencing, and expression studies of small intestinal and colonic mucosa.

Diet

Up to 70% of patients with IBS identify certain foods as symptom triggers, although linkage with a clear

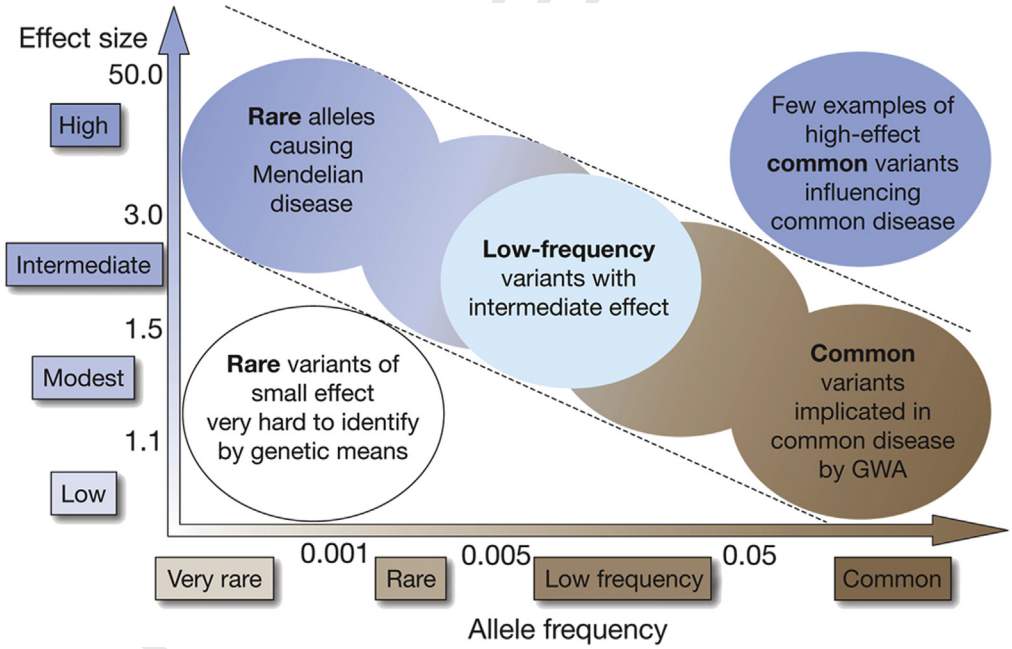

Figure 1. Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio).[4] There is a relationship between the allele frequency and effect size and the methods that are most appropriate for discovering gene–disease relationships.[4] Mendelian disorders (*upper left*) are typically caused by very rare alleles with a large effect size. This method requires large pedigrees available for testing and does not pinpoint the disease causing allele but a region that may contain hundreds of candidate genes. Other diseases (*lower right*) may be caused by a number of relatively common alleles, each of which increases the risk of disease by a small percentage. This class of disease has been studied with large case-control association studies, which search for the difference in allele frequency of polymorphic markers between unrelated groups of affected and unaffected individuals or within families. GWA, genome-wide association.

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