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At the End of the Beginning

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In the past decade, progress in the field of complex disease genetics has been accelerated by the HapMap project (<http://hapmap.ncbi.nlm.nih.gov/>), which led to the development of dense genotyping arrays, and by the availability of large DNA repositories of patients created by dedicated investigators. Such resources have led to the discovery of novel susceptibility loci of human disease by means of genome-wide association studies (GWAS). These “a priori studies” (a shift from the traditional approach of *hypothesis-specific* research) have allowed an unbiased method to decipher the genetic architecture of liver disorders.

In this issue of *Seminars in Liver Disease*, a group of experts: (1) summarizes the findings of recent genetic studies, including GWAS, in different liver diseases; (2) examines the scientific and clinical ramifications of these observations; and (3) proposes future methodological approaches to better delineate the genetic contribution in liver diseases. We are indebted to our contributors for superb reviews on the assigned topics. Mark Thursz and colleagues have written a synopsis on “Understanding the Host Genetics of Chronic Hepatitis B and C.” Traditional therapies for viral hepatitis have focused on the infectious agent. The recent identification of the *IL-28B* genotype as a major determinant of host treatment response and spontaneous resolution of infection of patients with hepatitis C virus is the best example of how genetic discoveries can revolutionize clinical practice. Christopher Day and colleagues have contributed a review on “Genetics of Alcoholic and Nonalcoholic Fatty Liver Disease.” Susceptibility and modifier genes of both entities are discussed, including genetic loci that participate in disease progression from steatohepatitis to fibrosis and to hepatocellular cancer. Gideon Hirschfield and Pietro Invernizzi provide an overview on “Progress in the Genetics of Primary Biliary Cirrhosis.” Two recent GWAS, as well as notable candidate gene studies, are reviewed and related to the pathogenesis of primary biliary cirrhosis with suggestions on future studies to better delineate this disorder. Frank Lammert and colleagues present an update on “Dissecting the Genetic Heterogeneity of Gallbladder Stone Formation.” Improving the understanding of subgroups of patients with gallstone disease could have significant clinical impact. Susceptibility genes for

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Dissecting the Genetic Contribution to Liver Disease; Guest Editors, Tom H. Karlsen, M.D., and Konstantinos N. Lazaridis, M.D.

gallstones are discussed along with ramifications of these observations on patient counseling. Jean-Charles Nault and Jessica Zucman-Rossi give an overview on “Genetics of Hepatobiliary Carcinogenesis.” Malignancy is a dreaded complication of advanced liver disease. Molecular pathways of carcinogenesis in both hepatocellular carcinoma and cholangiocarcinoma are discussed along with the promise of targeted therapies. Tom Hemming Karlsen and Arthur Kaser contribute a review on “Deciphering the Genetic Predisposition to Primary Sclerosing Cholangitis.” To date, the pathobiology of primary sclerosing cholangitis remains elusive. Functional annotations of the current disease loci are presented in an organized fashion as well as the challenges of translating these findings into clinical practice. Aftab Ala and Michael Schilsky have written a review on “Genetic Modifiers of Liver Injury in Hereditary Liver Disease.” This challenging topic covers Wilson disease, hereditary hemochromatosis, and α -1 anti-trypsin deficiency, and underscores the influence of genetics on disease variability as observed in the clinic. Finally, Brian Juran and Konstantinos Lazaridis provide a conceptual framework on “Genomics in the Post-GWAS Era.” The authors describe the lessons learned from the genome-wide association approaches, examine issues related to “missing heritability” and give an opinion on next generation genomics and personalized genetics for years to come.

In a recent article on translational research published by the National Human Genome Research Institute (<http://www.genome.gov/27530872>), it was stated that “. . . improved human health is a major goal of genomic research” Reviewing the recent genetic studies in liver diseases, as presented in this issue, it is apparent that a substantial amount of genetic information has already been accumulated. Yet, with a few exceptions, the opportunities for translational application knowledge are limited. Undoubtedly, the work of bridging the gap between the new genetic findings and their implementation in clinical practice is a challenging task for which the most efficient strategies remain to be defined. The barriers for such progress are multifaceted. For example, although a large number of disease susceptibility genes have been identified thus far, each appears to have small individual effect on disease, and several are involved in more than one clinical condition. This phenomenon probably attests the redundancy of biologic systems and likely represents the properties of the scientific tools applied in the discovery process, (i.e., the current association studies looking for frequent genetic variants [$>5\%$ in a population]). These variants often represent weak biologic effects with a selective advantage for which evolution has favored it, yet still subtle enough to make them redundant, inert, and without disadvantages in most settings. Such variants generate broad phenotypic features, thus yielding groups of “autoimmunity” or “cancer” genes, that are shared between what in the clinic are often appreciated as separate entities. Of course, the fact that the biologic effects from the common susceptibility variants can be classified as “weak” does not necessarily correlate with the translational potential. For instance, the peroxisome proliferator-activated receptor gamma susceptibility variants in type II diabetes have an odds ratio of less than 1.2,¹ yet glitazones, which have been shown to improve this condition, serve by activating this receptor. The lesson from this example is that what is seen by the statistics is merely the “tip of the iceberg” of potential clinical applications.

If we are then at the point of simply scratching the surface of liver disease genetics, what can we expect from the coming years? To make progress in the translation of research

observations in clinical practice, we need several parallel paths taken concurrently by the scientific community. First, efforts to better define the genetic architecture of liver disease within existing strategies should and will undoubtedly continue, fueled by the ever-increasing performance and decreasing costs of various genotyping technologies. However, the recent association study meta-analysis in Crohn's disease demonstrated that increasing the number of robust susceptibility loci from 32 to 71 merely enhanced the explained proportion of the disease heritability from 20 to 25%,² probably to the boundary of what the present genetic association studies can achieve. The answer to the 75% of “missing heritability” is likely to reside not only in rare causal variants of the genes already found³ or other loci,⁴ but also in gene–gene and gene–environment interactions, epigenetic risk factors, as well the complex influence of ethnic background.^{5,6} Strategies to define the role of these factors in human diseases are necessary.

Second, rather than simply applying “brute force” to increase sample size to detect further risk variants with odds ratios below 1.1, a rethinking on how we perform phenotyping is urgently needed. As shown by the poor overlap between susceptibility gene-based classification and clinical phenotyping in Crohn's disease,⁷ traditional medicine is likely to group cases in a manner that dilutes genetic risks and subsequently our chances of robust findings. How to maneuver in a refined direction more representative of molecular pathology is not clear for poorly characterized conditions. However, as suggested by the strength of the treatment response findings at *IL28B* in patients with chronic hepatitis C genotype 1 infection, the behavior of present tools is likely to improve in such a setting.

Ultimately, upcoming efforts are likely to improve genetic methods in the context of “personalized medicine.” With the advent of whole genome sequencing, data available for analysis will grow dramatically,^{8,9} as shown by the stable number of novel single nucleotide variants discovered per individual genome (~144,000 in recent applications).¹⁰ Refining this plethora of information in a manner that may aid clinical decision-making will be likely soon within our scope, but will require an even closer collaboration between these working in the clinic and those skilled with the technologies and bioinformatics. An important example is the appropriate application of therapeutics to a patient based on genetic susceptibility patterns and pharmacogenetic characteristics.

Better appreciation of the genetic architecture of complex liver disease has paved the way for new studies into pathogenesis and therapy. The scientific inquiry of liver disease genetics has taken us not to the end of our efforts, but to the end of the beginning.

REFERENCES

1. Zeggini E, Weedon MN, Lindgren CM, et al. Wellcome Trust Case Control Consortium (WTCCC). Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science*. 2007; 316(5829):1336–1341. [PubMed: 17463249]
2. Franke A, McGovern DP, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. *Nat Genet*. 2010; 42(12):1118–1125. [PubMed: 21102463]
3. Momozawa Y, Mni M, Nakamura K, et al. Resequencing of positional candidates identifies low frequency IL23R coding variants protecting against inflammatory bowel disease. *Nat Genet*. 2011; 43(1):43–47. [PubMed: 21151126]

4. Li Y, Vinckenbosch N, Tian G, et al. Resequencing of 200 human exomes identifies an excess of low-frequency non-synonymous coding variants. *Nat Genet.* 2010; 42(11):969–972. [PubMed: 20890277]
5. Eichler EE, Flint J, Gibson G, et al. Missing heritability and strategies for finding the underlying causes of complex disease. *Nat Rev Genet.* 2010; 11(6):446–450. [PubMed: 20479774]
6. Pulit SL, Voight BF, de Bakker PI. Multiethnic genetic association studies improve power for locus discovery. *PLoS ONE.* 2010; 5(9):e12600. [PubMed: 20838612]
7. Cleynen I, Mahachie John JM, Henckaerts L, et al. Molecular reclassification of Crohn's disease by cluster analysis of genetic variants. *PLoS ONE.* 2010; 5(9):e12952. [PubMed: 20886065]
8. Wheeler DA, Srinivasan M, Egholm M, et al. The complete genome of an individual by massively parallel DNA sequencing. *Nature.* 2008; 452(7189):872–876. [PubMed: 18421352]
9. Ashley EA, Butte AJ, Wheeler MT, et al. Clinical assessment incorporating a personal genome. *Lancet.* 2010; 375(9725):1525–1535. [PubMed: 20435227]
10. Pelak K, Shianna KV, Ge D, et al. The characterization of twenty sequenced human genomes. *PLoS Genet.* 2010; 6(9):e1001111. [PubMed: 20838461]