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Review

Role of genetics in diagnosis and therapy of acquired liver disease

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ABSTRACT

By implementation of novel genotyping technologies, progress in delineating the genetic architecture of acquired liver diseases has been achieved in recent years. The rapid dissemination of genome-wide linkage and association studies has paved the way for the identification of genetic variants that cause or modify non-viral liver diseases as well as the natural and treatment-related outcomes in chronic viral hepatitis. Invaluable genomic data has recently been derived from additional genome-wide association studies (GWAS) of the archetypical cholestatic liver diseases primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). Beyond providing novel pathobiological insights in need of more sophisticated functional annotation, gene variation might in the future be instrumental in precise risk stratification and the development of genotype-based treatment algorithms. In this regard, the definition of subtypes of acquired liver disease and re-categorization of clinically defined disease phenotypes into a more 'genometype'-based disease classification represents a priority future research direction.

Contents

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1. Introduction: Genomics in the GWAS era and beyond

In recent years, the accumulation of genomic information on disease susceptibility and progression has gained unprecedented momentum. The initial molecular genetic analyses focused on the identification of penetrant mutations underlying rare monogenic diseases (*Mendelian* traits) in individual patients or small groups of affected individuals, providing important advances into the pathobiological understanding of different hereditary liver diseases such as Wilson disease, haemochromatosis, and progressive familial intrahepatic cholestasis (PFIC types I–III). By contrast, the heritability of common (complex) liver diseases are not related to single-gene alterations but rather to a multitude of low-impact gene variants (odds ratios typically < 1.5), fine-tuned by gene–gene interactions (epistasis) and environmental factors and their complex higher order interactions (Fig. 1). The full-scale delineation of human sequence variation by the *Human Genome Project* and the *International Hap Map Project* and the recent refinements by the *Personal Genome Project* and the *1000 Genomes Project* has laid a sound foundation for the rapid dissemination of ever-increasing genetic information related to complex human traits and diseases (Abecasis et al., 2012). Accompanied by the plummeting costs, technological sophistication and broader accessibility of genotyping platforms, comprehensive mapping of genetic markers underlying acquired liver diseases by GWAS in large informative patient cohorts has become a reality in recent years (Krawczyk et al., 2010). By implementation of high-throughput platforms this unbiased, hypothesis-free approach renders scanning hundreds of thousands of single-nucleotide variants (SNVs) causing and/or modifying diseases across the whole genome feasible (Zimmer and Lammert, 2011b). This has been applied to various complex liver diseases, such as viral hepatitis, gallstone disease, non-alcoholic fatty liver disease (NAFLD) as well as cholestatic liver diseases (PBC, PSC), providing important novel pathobiological insights and information on genetic risk assessment for these diseases.

However, despite these major achievements of the GWAS approach there is still a substantial fraction of 'missing heritability' unaccounted for, which has been explained by incomplete tagging SNP coverage ('array blind spots'), rare variants

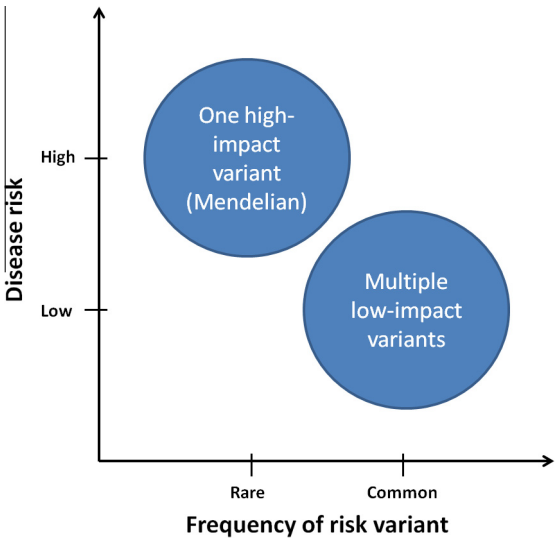

Fig. 1. Genetic risk model underlying categorization as rare (monogenic) and common (multifactorial) diseases. The inverse correlation between the frequency of disease susceptibility variants and the magnitude of their phenotypic impact (typically expressed as odds ratio, OR). In contrast to rare genetic diseases with causative mutations, there are multiple low-impact variants underlying common diseases ('common disease – common variant' concept).