International Research Journal of Biotechnology Vol. 14(2) pp. 1-3, April, 2023
Available online http://www.interesjournals.org/IRJOB

Mini Review

The Treatment of Liver Disease by the Use of Techniques of Genomics

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Received: 29-Mar-2022, Manuscript No. irjob-23-94833; **Editor assigned:** 31-Mar-2022, PreQC No. irjob-23-94833(PQ); **Reviewed:** 14-Apr-2022, QC No. irjob-23-94833; **Revised:** 19-Apr-2022, Manuscript No. irjob-23-94833(R); **Published:** 26-Apr-2023, DOI: 10.14303/2141-5153.2023.44

Abstract

The first 30 years of the Journal of Hepatology have paralleled significant advancements in our knowledge of liver function and disease. It has been greatly influenced by genetic advancements. Early research in the 1970s and 1980s revealed the significant links between autoimmune liver disorders and the major histocompatibility complex. The discovery of the genes in charge of Mendelian liver illnesses was sped up during the 1990s by advancements in genomic technologies. This has been possible over the past ten years. The discovery of new pathophysiological mechanisms, the necessity to reclassify liver illnesses, and the emergence of novel disease therapies have all been made possible by findings. Genetics will help with tailored medication in the near future and enable for deeper categorization of liver illnesses. It is difficult to apply quickly evolving technology in the clinical setting and to evaluate the vast amounts of genetic data that are amassing. The historical view of genetics in liver illnesses highlights the possibilities for upcoming clinical studies and patient management.

Keywords: Genetic advancements, Mendelian liver illnesses, Pathophysiological, Novel disease therapies

INTRODUCTION

Genetics has improved our comprehension and treatment of liver disease during the past 30 years. Positional cloning of unidentified disease genes, straightforward gene tests for Single Nucleotide Variants (SNV), Genome-Wide Association Studies (GWAS), which compare genotype frequencies across the entire genome between cases and controls to identify unknown genetic risk factors, and Next-Generation Sequencing (NGS) of specific genes, all exons, or the entire genome in individual patients are among the fundamental technologies available for genetic analysis **(BeLue R et al., 2016).**

Here, we address five important issues that can help students, researchers, and healthcare professionals comprehend the advancements in the genetics of liver disease in order to show the developments and prospects of these genetic methodologies and technologies. Our responses address both historical issues and demonstrate how improvements in our understanding have resulted in a fast evolving framework for diagnostic and treatment approaches. We want to provide the reader with essential instances of the current status of the field and our related reflections, rather than a comprehensive portrayal of the entire genetics of liver disease. We purposely ignore the role of genomics in the treatment of hepatocellular carcinoma and cholangiocarcinoma in favour of our focus on germline alterations **(Salama MS et al., 2021) (Li J et al., 2018)..**

The Wilson disease gene ATP7B and the haemochromatosis gene HFE were the first genes of monogenic disorders with major liver characteristics to be identified and cloned. By linkage disequilibrium and haplotype analysis on more than 100 families, the Wilson disease gene was located. It encodes a P-type ATPase gene having metal binding domains that are comparable to those in prokaryotic heavy metal transporters, according to functional investigations. Following up on this revelation, other previously unrecognised features of copper transport and the pathogenesis of Wilson disease were uncovered. A similar approach was used three years later to demonstrate that patients with autosomal-recessive haemochromatosis have mutations in the HFE gene of the extended major histocompatibility complex **(Cannata F**

et al., 2020) (Omar SM et al., 2018). In addition, several varieties of non-HFE hereditary hemochromatosis were later identified and associated to mutations in the ferroportin, transferrin receptor 2, hepcidin, and hemojuvelin genes, in that order. Together, these genetic findings opened the door to the complete characterization of hepatic iron metabolism and its regulators, enabling the analysis of the mechanisms behind the onset of liver illness in the presence of identified mutations.

Many disease genes have different mutation profiles. About 95% of people with hereditary hemochromatosis have a founder mutation, which is the most common cause of the disease. A distinct genetic profile is displayed in Wilson disease, with more than 500 mutations in the ATP7B gene having been reported as of yet. For this reason, focused genotyping of the dominant variants is used in haemochromatosis genetic testing, whereas gene sequencing and variant analysis are required in Wilson disease to obtain genetic support for the diagnosis **(Al-Rasheedi AAS et al., 2014).**

Gallstone disease was the subject of the first GWAS in hepatobiliary illnesses, which identified the hepatobiliary cholesterol transporter ABCG5/G8 as a key global susceptibility gene, with p.D19H as the most likely causal single nucleotide polymorphism. The monogenic disorder sitosterolemia, which is characterised by unrestricted intestinal absorption of both cholesterol and phytosterols like sitosterol, is thought to be caused by other uncommon loss-of-function SNVs in this transporter that have previously been found in specific patients. The neighbouring, antiparallel ABCG5/G8 genes produce two ATP-binding cassette hemitransporters, which are found in the apical membranes of enterocytes and hepatocytes. The situation also highlights a key distinction between risk factors for complex or polygenic traits against those that are monogenic **(Dong Q et al., 2019) (American Diabetes A 2019).** The SNVs seem to be enough to account for the sitosterolemia-related phenotype. Interacting genetic and environmental variables are necessary for gallstone formation for risk alleles of SNPs found by GWAS.

Several dozen risk genes for primary biliary cirrhosis, primary sclerosing cholangitis, and most recently, autoimmune hepatitis have been found by GWAS for autoimmune liver illnesses. The risk loci that have been identified largely coincide with those of other autoimmune and immune-mediated disorders **(Saeedi P et al., 2019).** This indicates that rather than liver afflictions specifically, the majority of the genetic risk factors for these symptoms involve an increasing vulnerability to autoimmunity. Strong MHC correlations and a significant portion of risk loci in PBC, PSC, and AIH both support the pathophysiological significance of adaptive immune responses. PBC, PSC, and AIH have generally minimal genetic contributions to illness susceptibility, with the current risk gene pool accounting for less than 10% of the total disease liability **(Barkai L et al., 2020).** This percentage will rise with more studies, but more than 50% of the vulnerability to these illnesses still likely has an environmental cause.

CONCLUSION

It is clear from the explanation above that genetic testing is already pertinent for monogenic and even oligogenic liver problems. Here, access to technology and the necessary knowledge are the barriers to clinical deployment. WES has now been effectively employed for research on a large scale. Compared to WES, whole-genome sequencing has both benefits and drawbacks. Complete genome coverage, simpler sample preparation, and less bias in the produced sequence all result in these advantages. Yield is therefore higher in terms of a definitive diagnosis. Although WGS is becoming more affordable, interpreting the data still presents significant obstacles to the broad adoption of either approach for routine diagnosis. There are now a variety of commercial software programmes, primarily for research purposes, but none of them is ideal, and there is no interaction with the standard patient information systems. The vast numbers of variants that are present in every person continue to be the most important problem. These variants contain the "cause" of Mendelian disorders as well as disease-modifiers and predictors of therapy response, as was previously mentioned. Every disease is ultimately more or less complex because disease severity varies even for "typical" monogenic liver diseases, making it challenging to distinguish between a susceptibility allele and a disease modifier. Simply put, we lack the expertise and resources necessary to apply the majority of the new findings to clinical practise. Large cohort studies including thorough clinical and molecular phenotyping together with the WGS data are the only way we will be able to approach this information and so get closer to a notion of "personalised treatment." These activities are more important than ever right now.

CONFLICT OF INTEREST

None

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