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Commentary

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# Importance of genetics in the age of direct acting antivirals against the Hepatitis C virus

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Hepatitis C virus (HCV) is one of the main causes of chronic liver disease, cirrhosis, hepatocarcinoma, liver transplantation and liver death [1].

Nearly 70 million people worldwide are chronically infected with HCV, many of them are unaware of their infection [1,2]. The natural history of Chronic Hepatitis C (CHC) is highly variable, in some cases having a relatively benign behavior, while in others it has a fast progression to hepatic cirrhosis and hepatocellular carcinoma (HCC). Current treatment with direct-acting antivirals (DAA) with very high efficacy (greater than 95%) has changed the natural history of HCV liver disease drastically. Despite the short time that these antiviral drugs have been used, they have shown a decrease in the appearance of cirrhosis and its complications, development of HCC, need for liver transplantation and mortality in patients who get virus elimination [3]. Additionally, they have also shown significant economic savings. On the other hand, HCV chronic liver disease can be associated with extrahepatic manifestations that also improve with viral eradication [4-6].

The Human Genome Project, initiated in 1990, achieved a draft of the genetic map in 2001 and was an important advance in the understanding of the genetic mechanisms of diseases [7]. The impact of genetic factors on the natural history of CHC and its implication in the response to treatment, has been an object of great scientific interest and many studies [8,9]. The study of genetic polymorphisms has led to multiple investigations often with relevant results [10].

In the last few years, single-nucleotide polymorphisms (SNPs) of the *IL28B* gene were extensively studied. A significant influence of certain *IL28B* SNPs was described both in the response to antiviral treatment [11-14] and in the evolution of acute hepatitis C [15,16] This discovery was of great importance at a time that antivirals were less effective and had significant adverse effects. In this context, the determination of *IL28B* SNPs was very useful to predict the possible response to treatment. Although at present this SNP has lost much of its importance [17], others can be very useful in the management of HCV liver disease [18].

Recently, our group found an association of certain SNPs of genes related to immune system and inflammation mediators, with the severity of HCV liver disease and its progression. Thus, polymorphisms of *CXCL9-11* were associated with the stage of fibrosis measured by transient elastography. On the one hand, heterozygosis (*CXCL9* rs10336 AG, *CXCL10* rs3921 CG and *CXCL11* rs4619915 AG) seemed to be a protective factor; while homozygosis for the minor allele (*CXCL9* rs10336 AA, *CXCL10* rs3921 CC and *CXCL11* rs4619915 AA) was a risk factor for liver fibrosis [19].

In addition, *IL7RA* polymorphisms were also associated with changes in transient elastography values and progression in fibrosis stages in patients infected with HCV, especially the *IL7RA* allele rs6897932 T that was associated with an increased risk of liver fibrosis progression and cirrhosis. *IL7RA* rs987106 showed a weaker association with the progression of liver disease while *IL7RA* rs3194051 did not [20].

Therefore, although current DAAs have been a transcendental change in treatment of HCV liver diseases, modifying substantially their natural history; genetic polymorphisms can be a very important tool in the management of HCV liver disease [21] and will be probably a key factor in the evolution of patients once the sustained viral response with antiviral treatment has been achieved.

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