GWAS reveals new genetic associations with liver fibrosis progression in HIV/HCV

Sigrd Le Clerc, Damien Uveling, Taoufik Labis, Maria Winockco, Joannis Théodorou, Laurent Abele, Yves Lévy, Dominique Salmon, Jean-François Zagury, Stéphanie Dominguez

Abstract

Background: Genetic studies with common variants in HIV mono-infection have mainly revealed associations with HIV-1 progression and adverse clinical outcomes in the host. In contrast, the genetic associations reported were found using imputed data and not on genotyped data. In this study, we used imputed SNPs to search for genetic determinants for liver fibrosis progression in HIV/HCV co-infected patients.

Methods: The patients analyzed in this study belonged to the large French ANRS CO13 HEPAVIH cohort of co-infected HIV/HCV patients to study these signals and search for additional markers with a potential impact on the disease. The patients were genotyped using the Illumina Omni2.5 BeadChip containing 2,391,739 SNPs. We performed a usual quality control: SNP genotyping >98%, patient genotyping >95%, Hardy-Weinberg equilibrium >10^{-8}, IBD <0.125, minor allele frequency >1%). A hierarchical approach was used to search for genetic association on stratification >1%. After quality control 922,971 SNPs and 439 patients were available for the association analysis.

Results

Stratification:

A total of 42 patients were excluded from the study because of either a large proportion of sequenced patients, or a genetic stratification was estimated by linear regression using as covariates the age at baseline, gender, the HCV genotype, the duration of infection was estimated from the presumed year of infection, and the duration of the antiretroviral treatment. Genetic stratification was also taken into account by adding as covariates the 2 censored (liver fibrosis < 9 kPa) events were defined, and the duration of infection was estimated from the presumed year of infection.

Association with liver fibrosis stage (in kPa)

For each SNP, we performed the usual analysis of the liver fibrosis stage measured in kPa in the additive model.

Three SNPs in two regions located on chromosome 3 were associated with liver fibrosis progression. The rs11790131-A allele favored a more rapid progression towards a fibrosis stage ≥ 9 kPa (Figure 1). The rs8056742-G allele favored a more rapid progression towards a fibrosis stage ≥ 9 kPa (Figure 2). The rs16975170-A allele favored a more rapid progression towards a fibrosis stage ≥ 9 kPa (Figure 3).

Discussion

Biological interpretation

The fine mapping of association with the quantitative liver fibrosis stage at inclusion (in kPa) identified 3 SNPs (rs16975170, rs11790131 and rs8056742) on chromosomes 1, 3, and 10 located within genes LOC392288, LOC101928135, and MAP1LC3BP1, respectively. The rs11790131-A allele is ~ 86 kb away from rs8056742-G allele. Moreover, there exist several SNPs in high LD with rs16975170 and rs8056742, located in a region with particular chromatin state in the eQTL database. The rs16975170-A allele is located in the gene KIAA0513, that encodes the MAP1LC3BP1 protein which is a component of the AAA ATPase family of proteins involved in autophagy. These SNPs are associated with more severe liver fibrosis progression in a region defined by a single SNP.

Conclusions

This preliminary GWAS study on the HEPAVIH cohort did not identify any markers associated with liver fibrosis progression. However, the study confirmed that the rs11790131-A allele is a major determinant of liver fibrosis progression in HIV/HCV co-infected patients. Future studies need to be performed to validate the biological hypotheses emerging from this preliminary GWAS study.

References

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