Conclusion and Next Steps The project has been a resounding success, well received by homeless PWID, hepatology treatment teams, hostal and homeless services, reflecting the constructive impact on collaborative working. Birmingham Operational Delivery Network (ODN) has planned to introduce the model across the West Midlands, with additional peer support capacity to engage homeless PWID through workshop delivery prior to testing and to facilitate treatment starts.

EXPLORING GENETIC VARIATION OF PDCD1, WHICH ENCODES T-CELL RECEPTOR PD-1, IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND HEPATOCELLULAR CARCINOMA (HCC)

Within the common etiologies of chronic liver disease associated with HCC development, environmental and genetic factors contribute to individual susceptibility. Our focus was on NAFLD-HCC, where older age, male sex, diabetes and cirrhosis elevate risk. In addition, single nucleotide polymorphisms (SNPs) in genes that regulate fat storage or metabolism in the liver (PNPLA3 and TM6SF2), further elevate NAFLD-HCC risk. Hypothesising that an immune response to steatosis is key, we have explored SNPs in candidate immunoregulatory genes, including MICA, CD44, and PDCD1, which encodes for the T cell receptor, PD-1.

Methods SNPs in the candidate genes (PNPLA3rs738409; TM6SF2rs2596542; MICArs2596542; CD44rs187115; PD-1 rs7421861 and rs10204525), determined by taqman assay or GWAS, were analysed in silico studies indicate that PD-1 rs7421861 is an intronic SNP that disrupts putative alternative splice sites, potentially promoting full length transcript expression. The ‘T’ allele of PD-1 rs10204525 is an intronic SNP that disrupts putative alternative splice sites, potentially promoting full length transcript expression. The ‘T’ allele of PD-1 rs10204525 is reportedly associated with higher levels of PD-1 expression in HBV infection. While this allele is rare in Europe, its prevalence is much higher (66%) in Asian populations.

Discussion In combination, these studies suggest that while particular variants of PD-1 may vary in different populations, those that promote elevation of PD-1 in T cells – associated with impaired T cell function - may elevate CLD HCC risk.

A GENOME-WIDE ASSOCIATION STUDY OF SEVERE ALCOHOLIC HEPATITIS

Alcoholic liver disease (ALD) is a complex disorder, resulting from the interplay of environmental and genetic factors. Severe alcoholic hepatitis (AH) is an acute clinical manifestation of ALD, which has a high associated mortality but develops in only a minority of patients, estimated to be 6%.

Results The genotype frequencies of the candidate SNPs in the Newcastle cohort (figure 1), confirmed significant HCC associations for the variant alleles of PNPLA3 and TM6SF2. A novel association for PD-1 rs7421861 allele A was also identified (p<0.001), which was independent of age, sex, cirrhosis and diabetes (P=1.53E-03, lnOR -0.72). Notably, this highly significant association in the Newcastle cohort was weakened when combined by meta-analyses with the Berne and Milan cohorts (P>0.05). However, in the combination meta-analyses (Newcastle and Berne), a significant and independent association for the ‘T’ allele of PD-1 rs10204525 with NAFLD-HCC risk emerged (p=0.02, lnOR=0.63), attributable largely to a risk in women (present in 39.5% of NAFLD-HCC females, versus only 17.1% males). In silico studies indicate that PD-1 rs7421861 is an intronic SNP that disrupts putative alternative splice sites, potentially promoting full length transcript expression. The ‘T’ allele of PD-1 rs10204525 is reportedly associated with higher levels of PD-1 expression in HBV infection. While this allele is rare in Europe, its prevalence is much higher (66%) in Asian populations.

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