Conclusion and Next Steps The project has been a resounding success, well received by homeless PWID, hepatology treatment teams, hostel 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.

07 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)

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Background 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 (PNPLA3 rs738409; TM6SF2 rs2596542; MICA rs2596542; CD44 rs187115; PD-1 rs7421861 and rs10204525), determined by tagman assay or GWAS, were analysed in a Newcastle cohort (420 NAFLD, 203 NAFLD-HCC patients). To determine if SNP associations were independent of age, sex, cirrhosis and diabetes status, these were sequentially included as covariates for logistic regression. 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.

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.
<15%. An understanding of the genetic factors underlying severe AH may be essential to improving risk-stratification and identifying novel therapeutic targets for this understudied syndrome.

Method Cases with severe AH were recruited from the UK Steroids or Pentoxifylline trial (STOPAH) (n = 812). Controls with a history of alcohol dependence but without evidence of significant liver injury were recruited from Centre for Hepatology, Royal Free Hospital, London (n = 936). All participants were of white British/Irish descent. DNA was genotyped using two platforms Illumina HumanCoreExome BeadChip (Illumina, San Diego, USA) and Illumina PsychArray Beadchip (Illumina, San Diego, USA). Separate GWAS analyses were undertaken on each array using Plink v1.9 followed by meta-analysis in METAGENOMICS.

Results The variant rs738409 in PNPLA3 was associated with severe AH at genome-wide significance (PTHRESHOLD<5 × 10−8; P = 6.66 × 10−12; Z score = 6.865). Three additional independent risk loci were identified at the suggestive significance threshold, in ATP2C2 (PTPase Secretory Pathway Ca2+ Transporting 2), (PTHRESHOLD<1 × 10−5; PMETA = 4.33 × 10−7; Z score = 5.054), PHYH (Phytanoyl-CoA 2-Hydroxylase) (PMETA = 3.16 × 10−6; Z score = 4.66) and ANGPT1 (Angiopoietin 1) (PMETA = 5.12 × 10−6; Z score = -4.56). In addition, nine gene-sets were identified at statistical significance (PBON < 0.05) involving pathways associated with sterol regulatory element-binding protein signalling (PBON = 1.21 × 10−5), interleukin 17 secretion (PBON = 1.01 × 10−4) and regulation of natural killer T cell proliferation (PBON = 1.88 × 10−4).

Conclusions The pivotal role of PNPLA3:rs738409 in determining the risk for developing severe AH was confirmed in this study. In addition, potential risk loci were identified in ATP2C2, which encodes a Mn+/Ca2+ transporter and is highly expressed in the gastrointestinal tract; PHYH which is implicated in phytanic acid metabolism; phytanic acid binds to and/or activates the transcription factors PPAR-alpha and retinoid X receptor; and ANGPT1 which encodes the angiogenic promoter angiopoietin 1. Additionally, a number of potential pathways were identified, through gene set analysis, which appear to be involved in severe AH, influencing lipid metabolism and inflammation. These novel findings open new avenues for investigation and therapeutic endeavour.

Background Acute liver failure (ALF) remains a rare but life-threatening condition which requires early prognostication for transplantation (LTx). Existing models such as the King’s College Criteria (KCC) lack sensitivity. We have previously demonstrated the potential for regeneration linked miRNA to perform as biomarkers in acute and chronic liver disease. The aim of this study was to develop a miRNA-based prognostic model for acetaminophen (APAP) ALF.

Methods Samples were provided by the US ALF Study Group. We assessed serum miRNA expression from 193 patients (94 survivors, 89 non-survivors) with APAP-ALF at two time points (early; day 1, late; day 3−5). Transplanted patients were excluded. A panel of 24 miRNA identified from our previous studies were analysed. Multiple logistic regression was used to create early and late miRNA outcome prediction models. Clinical data were incorporated to improve prognostication.

Results Early up-regulation of miR-150 and down-regulation of -16-2 were associated with mortality. The early detection of miR-20a and absence of miR-149 were associated with mortality. Late up-regulation of miR-30a and down-regulation of -122, 16-2 and -21 were significantly associated with mortality. Late detection of miR-149, -17 and -191 were associated with mortality. Prognostic models were made for early and late miRNA expression. The early model contained miRNA associated with regeneration (miR-20a, -27a, -140, -150, -191) and achieved an area under the receiver operator curve (AUC) of 0.78 (95% CI 0.71−0.84, p<0.0001). This model was enhanced when combined with the Model for End-Stage Liver Disease score (MELD) and vasopressor requirement (AUC 0.83, 95% CI 0.78−0.89, p<0.0001). The late model contained miRNA associated with cell death (miR-16-2, -30a, -122, -149, -191) and achieved an AUC of 0.83. (95% CI 0.76−0.89, p<0.0001). This model was enhanced when combined with MELD and vasopressor requirement (AUC 0.91, 95% CI 0.86−0.96, p<0.0001). Conventional outcome prediction models performed as follows; KCC (early AUC 0.60, 95% CI 0.48−0.73, p=0.07, late AUC 0.69, 95% CI 0.56−0.82, p<0.01), MELD (early AUC 0.72, 95% CI 0.64−0.79, p<0.0001, late AUC 0.86, 95% CI 0.80−0.91, p<0.0001) and ALF Study Group Prognostic Index (early AUC 0.76, 95% CI 0.69−0.83, p<0.0001, late AUC 0.88, 95% CI 0.82−0.94, p<0.001).

Conclusion We demonstrate that specific serum miRNA have prognostic value as biomarkers in ALF. Our early model utilised regeneration linked miRNA whereas our late model utilised cell-death linked miRNA; this may signify mechanistic differences at early and late time points which determine patient survival.

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