Abstract P09 Table 1

	Training cohort AUROC (95% CI)	Validation cohort AUROC (95% CI)
NAS 0–2 vs NAS 3–8	0.833 (0.700 to 0.966)	0.829 (0.737 to 0.921)
NAS 0–3 vs NAS 4–8	0.854 (0.763 to 0.945)	0.784 (0.668 to 0.900)
NAS 0–4 vs NAS 5–8	0.865 (0.772 to 0.957)	0.723 (0.505 to 0.941)

for ascertaining prognosis and the stratification of patients for existing interventions and emerging therapies. Liver biopsy is considered the reference standard for assessing NASH. The aim of this study was to develop a biomarker of NASH which would be able to detect NASH prior to the development of significant hepatic fibrosis. Candidate biomarkers of hepatic inflammation, apoptosis and liver fibrosis were selected on the basis of biological plausibility and previous association with NAFLD.

Method 172 patients with NAFLD and no evidence of other liver disease were consecutively recruited from two centres. 84 patients from the first centre were included as a training cohort and 88 patients from the second centre as a validation cohort. Liver biopsies were performed on all patients and scored using the NAFLD activity score (NAS). 36 patients with advanced fibrosis were excluded from the analysis. Serum samples were taken on all patients and tested for five matrix proteins (HA, P3NP, TIMP-1, Procollagen 4 and YKL-40) and 19 haematological and biochemical parameters including HOMA-IR. Stepwise multiple linear regression was used to determine the relationship of the multiple variables to the NAS score.

Results A model combining terminal peptide of pro-collagen III (P3NP) and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) was found to significantly correlate with the NAS score in the training cohort (R=0.643, R2=0.413, p<0.0000001). The regression model was then validated in the second patient cohort. AUROC were calculated for the ability of the model to discriminate between differing degrees of NAS.

Conclusion This model appears to have good diagnostic performance for the detection of NASH in both the training and validation cohorts. Our results appear promising and if confirmed in further studies this model will be of clinical utility in detecting the minority of patients with NAFLD who have NASH and are at risk of developing progressive liver disease.

P10 WHOLE-EXOME-SEQUENCING-BASED DISCOVERY OF NOVEL SYNDROMIC FORM OF NEONATAL CHOLESTASIS

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Introduction Two cousins from a consanguineous family presented with low γ glutamyl transferase (GGT) cholestasis, trichorrhexis nodosa (TN) and severe hypoglycaemia which required diazoxide to stabilise. One child also had life threatening diarrhoea necessitating parenteral nutrition, which suggested the possible diagnosis of trichohepatoenteric syndrome (THES). However screening of the THES gene (*TTC37*) excluded mutations.

Aim The aim of this study was to identify the molecular genetic defect in this family and hence further understanding of unexplained cholestasis within a multisystem disorder.

Method We used a novel combination of autozygosity mapping combined with whole-exome-sequencing (WES). An Affymetrix 250K SNP chip genome-wide linkage scan was used to identify common regions of shared homozygosity. SureSelect human All Exon kit (Agilent Technologies) and Illumina GaIIx was used for WES of both individuals. Single nucleotide substitutions and small insertion deletions were identified. Filtering of variants for novelty was performed by comparison to dbSNP131 and 1000 Genomes pilot SNP calls (March 2010) and variants identified in 40 control exomes sequenced and analysed by the same method described above.

Results The largest overlapping autozygous regions were at chromosome 7, 16, 20, 12 and 4. The whole exome sequencing identified 17 844 and 17 867 variations in patients 1 and 2 respectively. Of these only three homozygous non-synonymous variants and one frameshift variant were found in both patients in the identified homozygous regions. The frameshift was a homozygous single base G deletion (c.587delG) in exon 6 of *AKR1D1* which mapped within the candidate homozygous region in chromosome 7. The variant results in a frameshift at amino acid 196 leading to a premature stop codon 11 amino acids downstream (p. Cys196SerfsX11).*AKR1D1* encodes the enzyme δ^4-3-oxosteroid 5β-reductase that is required for the synthesis of chenodeoxycholic and cholic acids important for normal bile flow. Mutations in *AKR1D1* have previously been described in patients with severe neonatal liver disease.

Conclusion In conclusion we have extended the clinical features of bile salt synthesis disorders resulting from mutations in *AKR1D1* to include a severe form of low GGT cholestasis, TN and severe hypoglycaemia which may be amenable to treatment with bile salt supplementation. Combining the technique of whole genome linkage mapping and WES creates a powerful tool to elucidate the molecular basis of uncharacterised genetic disorders.

P11 INDUCTION OF HYPERAMMONAEMIA FROM THE SMALL AND LARGE INTESTINE IN PATIENTS WITH CIRRHOSIS WITH MAGNETIC RESONANCE QUANTIFICATION OF BRAIN WATER AND METABOLITES

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Introduction Induction of hyperammonaemia from glutaminase action in the small intestine[1] or systemic catabolism of oral amino acids[2 3] is well recognised but, although suggested in 1959 by Walser and Bodenlos,[4] ureolysis resulting in hyperammonaemia has not been demonstrated from urea delivered to the colon. Hepatic encephalopathy (HE) is now thought to be caused by cerebral oedema.

Aim We hypothesised that if hyperammonia is a key factor in hepatic encephalopathy, induced hyperammonaemia from oral amino acid or urea challenge would lead to transient changes in brain water distribution and metabolite concentration.

Method Amino acid (mixture of equal parts of glycine, serine and threonine) or urea challenges were undertaken in 18 patients with stable cirrhosis 5 of whom gave a history of hepatic encephalopathy. Sequentail blood ammonia concentration was determined with the ammonia checker and brain water and metabolites with magnetic resonance diffusion tensor imaging and spectroscopy.

Results Oral urea and amino acids (delivered to the colon by coating) resulted in peak increments in blood ammonia of 146±SD 164 and 55±51 μmol/l while for uncoated amino acids the mean increment was 58 (±41) μmol/l. The latter was accompanied by a significant increase in ADC of 9% (p=0.004). Increased ADC was significantly correlated with blood ammonia (r=0.58, p=0.04). The change in ammonia levels also correlated with the increase in