Introduction Identifying the underlying cause of liver disease is important, however in 5–30% of patients with cirrhosis no cause can be found, which is referred to as cryptogenic cirrhosis (CC). From registry data 4% of liver transplants are performed for CC. UK Transplant Registry data suggests CC recipients have a lower 1-year and 5-year survival than the national rate.

Understanding of the genetics underpinning liver disease has evolved significantly. More recently whole exome sequencing (WES) has been proposed for the evaluation of cryptogenic liver disease.

We sought to evaluate the diagnostic work-up of patients listed for transplant in the UK with CC, with a specific focus on the use of genomics.

Method A retrospective search of the UK Transplant Registry was performed for adult elective NHS patients registered for first liver transplant at 6 transplant centres between 1/1/15 and 31/12/20. Patients with CC or genetic liver disease as an indication at registration were included. Clinical information and results of diagnostic tests were collected.

Results After exclusion of 59 patients (42 genetic co-factor, 17 alternate aetiology), 228 patients were included: 120 CC, 4 diagnosed with genetic liver disease during assessment, 104 known genetic liver disease.

The patients without previously known genetic liver disease (n=124) had a median age at onset of liver disease of 49 years (IQR, 37–56), 82 (66%) were male, 16 (13%) had a family history of liver disease. Median age at listing was 55 years (IQR, 42–62), UKELD 56 (52–59) and MELD 15 (12–20). Prior diagnostics included: liver biopsy 80 (65%), cross sectional imaging 123 (99%), and cholangiography 26 (21%).

A genetic test was performed in 29 (23%) patients: 10 ATP7B, 20 HFE, 9 cholestasis gene panel, and 1 underwent WES. There were 4 new diagnoses of genetic liver disease made during evaluation: 2 MDR3 deficiency, 1 Wilson disease, 1 alpha-1-antitrypsin. In 2 other patients there were ABCB4 variants of uncertain significance and potential MDR3 deficiency.

Discussion Genetic sequencing is performed in selected patients assessed for transplant with CC, and in some cases a new diagnosis of genetic liver disease has been made. With increasing access to genetic testing and the NHS Long Term Plan to offer whole genome sequence as routine care, more

widespread use of genetic testing in patients with CC listed for transplant should be considered.

P066

DNA METHYLATION DIFFERENCES AND METHYLATION QUANTITATIVE TRAIT LOCI IN PRIMARY SCLEROSING CHOLANGITIS AND IGG4-RELATED SCLEROSING CHOLANGITIS

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10.1136/gutjnl-2021-BASL.75

Primary sclerosing cholangitis (PSC) and IgG4-related sclerosing cholangitis (IgG4-SC) are fibro-inflammatory conditions of the liver and biliary tree, driven by a complex interplay of genetic, environmental, and immunologic factors. Epigenetic studies sit at the interface between genes and the environment. In previous work we have defined replicable alterations in new-onset adult (Ventham et al, *Nat Commun* 2016;7:13507) and paediatric inflammatory bowel disease (Adams et al, *Inflamm Bowel Dis* 2014;20:1784). We have now assayed methylomes of patients with PSC and IgG4-SC to ascertain epigenetic signatures that may provide insight into pathogenesis and novel biomarkers, and compared these with the methylome of ulcerative colitis (UC) and healthy controls (HC).

DNA methylation profiling in whole blood and genotyping was performed in 70 PSC, 56 IgG4-SC, 66 UC, and 88 HC samples, with Infinium MethylationEPIC and Global Screening arrays (Illumina). UC patients were selected to match the clinical characteristics (extent, activity) of the PSC-UC cohort. Analysis was performed with R (v4.0.3). DNA methylation data was processed with Minfi, batch effects were treated with ComBat and associations were tested using limma. Genotyping was analysed with Plink (v1.9) and meQTLs with linear models in R. Statistical significance was determined using the Holm method.

Compared to HC, 31 probes showed significant methylation differences in PSC, and 13 in IgG4-SC, with 8 probes shared between conditions. In separate subanalyses of PSC-UC and PSC without IBD (n=13) we found 25 significant probes

Abstract P065 Table 1 Demographics, clinical characteristics and biochemistry of study population at time of listing for transplant

	Cryptogenic cirrhosis	Alpha-1-antitrypsin	Haemochromatosis	Cystic fibrosis	Wilson disease	MDR3 deficiency
Number	120	42	41	10	9	5
Age at listing median (IQR), years	56 (44–63)	54 (49–63)	61 (58–68)	28 (23–37)	31 (25–36)	31 (27–40)
Male%	78 (65%)	32 (76%)	36 (88%)	6 (60%)	6 (67%)	4 (80%)
BMI median (IQR), years	27.5 (23.9–30.9)	30.0 (25.1–35.8)	28.2 (25.9–31.6)	19.8 (19.2–20.7)	22.2 (21.2–28.9)	23.4 (22.3–24.8)
HCC%	17 (14%)	5 (12%)	26 (63%)	0	0	0
MELD median (IQR)	15 (12–20)	15 (12–19)	11 (7–14)	12 (10–14)	21 (14–28)	21 (17–25)
UKELD median (IQR)	56 (52–59)	55 (52–57)	51 (48–55)	54 (50–55)	56 (53–66)	64 (58–66)
ALT median (IQR), IU/L	41 (24–57)	41 (29–54)	32 (24–39)	35 (14–59)	84 (42–408)	142
AST median (IQR), IU/L	63 (47–85)	71 (56–99)	63 (39–78)	39 (32–42)	88 (60–133)	238 (113–369)
ALP median (IQR), IU/L	154 (116–241)	144 (107–177)	115 (89–154)	190 (90–385)	107 (90–149)	303 (189–618)
GGT median (IQR), U/L	84 (41–144)	68 (36–129)	72 (40–111)	80 (36–339)	112 (36–197)	151 (68–211)

Abstract P066 Table 1

Chr	Coordinate	Gene	PSC	IgG4-SC	UC
5	93905427	C5orf36	7.02×10^{-17}	4.45×10^{-12}	7.32×10^{-17}
3	101443535	CEP97	6.66×10^{-15}	2.62×10^{-12}	-
17	7481193	EIF4A1; SNORA67	8.48×10^{-13}	-	1.44×10^{-9}
3	101443691	CEP97	4.54×10^{-11}	-	-
4	89300650	HERC6	8.17×10^{-11}	4.37×10^{-9}	-
17	42075116	PYY	3.25×10^{-10}	7.8×10^{-10}	1.64×10^{-14}
19	797342	PTBP1	7.78×10^{-10}	-	6.16×10^{-14}
4	48136298	TXK	2.89×10^{-9}	-	-
3	96338474		4.97×10^{-9}	2.59×10^{-8}	-
8	125313885		6.94×10^{-9}	3.85×10^{-8}	-
4	48136234	TXK	6.34×10^{-8}	-	4.91×10^{-8}
21	34696571	IFNAR1	-	3.19×10^{-10}	-
3	169489583	MYNN	-	1.13×10^{-8}	-

in PSC-UC (6 not found in combined PSC) and 4 significant probes in PSC without IBD, of which only one was shared with PSC-UC. Analysis of the epigenetic clock did not show any age acceleration in PSC or IgG4-SC compared to healthy controls. Genotyping data revealed a strong signal in the HLA region in PSC, not observed in the other groups, though no findings were significant genome-wide as this study was underpowered as a GWAS. However, meQTLs in PSC were also strong in the HLA region with 19/40 significant findings in 4 clusters (HLA-DRB1, BTNL2, CSNK2B, and SFTA2). There was no overlap with the 36 significant meQTLs found in IgG4-SC. Of the significant disease-associated methylation differences PYY, involved in gut mobility and pancreatic secretion, and Interferon receptor subunit IFNAR1 stand out as targets for further investigation.

This study provides a novel description of whole-blood methylomes in PSC and IgG4-SC, and correlations with genetic variants. Future studies are needed to establish relationships with gene expression, and outcome measures.

Selected significant disease-associated methylation changes in PSC, IgG4-SC, and UC. P values are unadjusted, - denotes non-significance after Holm correction for multiple testing.

P067

OUTCOMES IN PATIENTS WITH ACUTE LIVER FAILURE TREATED WITH LOW VOLUME PLASMA EXCHANGE: UK MULTICENTRE EXPERIENCE

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10.1136/gutjnl-2021-BASL.76

Introduction Organ availability remains a barrier to successful management of patients with acute liver failure (ALF). Many patients have contra-indications to transplantation, leaving an ongoing unmet need for alternative and bridging therapies. High volume therapeutic plasma exchange (HV-TPE) has shown promising results in improving survival. In this multi-centre retrospective analysis from the United Kingdom (UK) we present the largest cohort to date of patients undergoing therapeutic plasma exchange (TPE) for the treatment of ALF, using substantially smaller volume exchanges (LV-TPE) than previously studied.

Methods Consecutive patients admitted to 5 transplant centre intensive care units (ICU) and receiving TPE treatment for ALF between June 2013- July 2020 were included. Treatment with TPE was based on judgement of the treating clinicians. Clinical and biochemical parameters were recorded on admission and following the final TPE. Outcome measures included changes in the biochemical, physiological and organ function status, overall survival and transplant free survival.

Results 120 patients received TPE treatment for ALF. Median age was 38 (30–52) and 59% (n=71) were female. The majority (72.5%) had ALF due to paracetamol overdose and

Abstract P067 Figure 1