High producer variant of lipoprotein lipase may protect from hepatocellular carcinoma in alcohol-associated cirrhosis

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UK Biobank: phenotype definitions.

Phenotypes used in our analysis of the UK biobank cohort were defined as follows:

HCC:

As detailed in the main text, HCC cases were identified by the presence of the ICD10:C22.0 code in a hospital admission, cause of death, or a cancer registration record, either before or after enrolment into UKB. Individuals without HCC were defined as controls

Cirrhosis:

Cirrhosis was defined as either: a) an in-patient hospital admission for cirrhosis of the liver; or b) a cirrhosis related death. These events were identified using a validated set of International Classification of Disease (ICD) & Operations/Procedure (OPCS4) codes.[1]. See table below:

Table S1 ICD10 and OPCS4 codes used to define cirrhosis

Code type	Code	Description
ICD 10 (relating to hospital admission and mortality events)	K70.3	Alcoholic cirrhosis of liver
	K71.7	Toxic liver disease with fibrosis and cirrhosis of liver
	K72.1	Chronic hepatic failure
	K74.4	Secondary biliary cirrhosis
	K74.5	Biliary cirrhosis, unspecified
	K74.6	Other and unspecified cirrhosis of liver
	K76.6	Portal hypertension
	I85.0; I859; I98.2	Esophageal varices
	I86.4	Gastric varices
OPCS4 (relating to hospital admissions only)	J06.1	Tranjugular intrahepatic insertion of stent into portal vein
	J06.2	Transjugular intrahepatic insertion of stent graft into portal vein
	G10.4	Local ligation of varices of oesophagus
	G10.8	Other specified open operations on varices of oesophagus
	G10.9	Unspecified open operations on varices of oesophagus
	G14.4	Fibreoptic endoscopic injection sclerotherapy to varices of oesophagus
	G17.4	Endoscopic injection sclerotherapy to varices of oesophagus using rigid oesophagoscope
	G43.7	Fibreoptic endoscopic rubber band ligation of upper gastrointestinal tract varices
	T46.1*	Paracentesis abdominis for ascites
	T46.2*	Drainage of ascites not elsewhere specified

ICD-10 refers to International Classification of Disease version 10. OPCS4 refers to Operation/procedure codes version 4. A hospital admission was considered to be due to cirrhosis morbidity if any of the above codes were present in the admission record. However, OPCS4:T461 and OPCS4:T462 (codes relating to ascites) are the exceptions to this rule. Here, these codes were only considered to reflect cirrhosis morbidity if accompanied by at least one corroborating ICD code for chronic liver disease (i.e. ICD10: K70-K77). This is because ascites can have non-hepatic causes.

Type 2 diabetes (T2DM):

Although UKB participants were asked about diagnosis of diabetes mellitus (UKB Field ID: 2443), they were not asked specifically about T2DM. Thus, we inferred T2DM status by taking all individuals who reported a diabetes diagnosis (UKB Field ID: 2443), excluding those with evidence of non-type 2 diabetes. Evidence of non-type 2 diabetes was based on either: 1) self-reported type 1 diabetes in UKB nurse interview; OR; 2) hospital admission for type 1 diabetes (ICD10: E10); OR 3) self-reported gestational diabetes (UKB field ID: 4041).

FIB4 index:

Fibrosis 4 (FIB4) index was calculated according to the formula:
(age[years]*aspartate aminotransferase[U/L])/(platelet count [10^9 cells/L]*sqrt(alanine aminotransferase[U/L]))

Other phenoypes:

All remaining phenotypes were derived directly from UKB fields. See table below.

Table S2 UKB field IDs and web links

Phenotype	UKB field ID	Showcase web link
Body mass index	23104	https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=23104
Alanine aminotransferase	23460	https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=30620
aspartate aminotransferase	30650	https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=30650
Cholesterol	30690	https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=30690
Glycated haemoglobin (HbA1c)	30750	https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=30750
Liver fat content	22436	https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=40061
Triglycerides	30870	https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=30870

Table S3 SNP-SNP interactions of LPL rs13702 and PNPLA3 rs738409 concerning the risk of HCC

Parameter	P	OR	95% CI	
			Lower	Upper
LPL rs13702 CC	0.024	0.123	0.020	0.754
PNPLA3 148M	0.000	1.658	1.370	2.006
LPL CC by *PNPLA3 148M*	0.129	1.899	0.830	4.347
Constant	0.000	0.242		

P value for SNP-SNP interaction was calculated by the multiplicative model

Supplementary reference

[1] Ratib, S., Fleming, K. M., Crooks, C. J., Walker, A. J. & West, J. Causes of Death in People with Liver Cirrhosis in England Compared with the General Population: A Population-Based Cohort Study. *Am. J. Gastroenterol.* 2015;110:1149-58.