Letter to the Editor

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The *MBOAT7* variant rs641738 alters hepatic phosphatidylinositols and increases severity of non-alcoholic fatty liver disease in humans

To the Editor:

We have recently shown in 125 subjects that insulin resistance and the *PNPLA3* I148M gene variant, two common risk factors of NAFLD, are characterized with markedly different content and composition of lipids in the human liver [1]. In 2015, a variant in membrane bound O-acyltransferase domain containing 7 (*MBOAT7*) at rs641738 was discovered to increase the risk of alcohol-related cirrhosis [2]. This variant was also shown to increase the risk of steatosis and histologic liver damage in NAFLD, independent of obesity [3]. The variant allele was common with a population prevalence of 58–67% and characterized by decreased hepatic gene and protein expression of MBOAT7 [3]. *MBOAT7* is also known as lysophosphatidylinositol acyltransferase 1 (*LPIAT1*), which catalyzes acyl-chain remodeling of phosphatidylinositols (PIs) [4]. Consistent with this function, plasma lipidomics analyses showed that amongst various lipid classes (triglycerides, cholesteryl esters, phospholipids, ceramides and sphingomyelins), only concentrations of PIs were altered [3]. Specifically, plasma concentrations of PI (36:4), PI (38:3) and PI (38:5) were decreased in proportion to the number of *MBOAT7* variant alleles, while most other PIs were increased [3].

To study effects of genetic variation in *MBOAT7* on human liver histology and lipidome, we genotyped the subjects in our previous study at rs641738 [1]. The subjects were consecutive patients undergoing bariatric surgery recruited using the inclusion and exclusion criteria described in [1]. The liver lipidome was analyzed using ultra-high performance liquid and gas chromatography combined with mass spectrometry and histology as described [1]. DNA was available from 115 subjects (age 48.0 ± 0.8 years, BMI 45.4 ± 0.5 kg/m^2, 67 % women), who were divided into three groups based on their *MBOAT7* genotype at rs641738 (n = 35 for CC, n = 60 for CT, n = 20 for TT).

The MBOAT7 genotype groups were similar with respect to age, gender, BMI, waist circumference, *PNPLA3* I148M and *TM6SF2* E167K genotypes (data not shown).

Steatosis (% of grades 0/1/2/3 were 23/60/3/14, 25/62/12/2 and 20/55/25/0, $p = 0.03$ in CC, CT and TT groups) and necroinflammatory (% of grades 0/1/2/3 were 74/26/0/0, 87/13/0/0 and 60/35/0/5, $p = 0.04$) grades differed significantly between the MBOAT7 groups. The prevalence of significant fibrosis (F2-4) increased with number of *MBOAT7* variant alleles (0 *vs.* 5 *vs.* 25 %, $p = 0.001$, Fig. 1). Of 7 different PIs in the human liver, PI (36:4) and PI (38:3), i.e., the same PIs as in the plasma in the study of Mancina and Dongiovanni *et al.* [3], decreased significantly as a function of the number of *MBOAT7* variant alleles, while the concentration of PI (40:5) increased (Fig. 1). All other lipid classes in the human liver (triglycerides, cholesterol esters, ceramides, sphingomyelins, hexosylceramides, phospholipids, and free fatty acids) were similar between the groups (data not shown). Fasting insulin (13.7 [8.4–17.1], 11.2 [6.5–18.3] and 12.3 [7.0–18.8] mU/L in CC, CT and TT groups), glucose (5.9 [5.0–6.6], 5.8 [5.4–6.6] and 5.7 [5.1–6.1] mmol/L), triglycerides (1.24 [1.06–1.55], 1.29 [0.91–1.69] and 1.08 [1.00–1.59] mmol/L), HDL (1.15 [0.98–1.33], 1.09 [0.93–1.38] and 0.98 [0.86–1.13] mmol/L) and low density lipoprotein (2.5 [1.9–3.4], 2.3 [1.7–2.9] and 2.4 [1.5–3.5] mmol/L) cholesterol concentrations were similar between the groups.

We thus replicate effects of the *MBOAT7* variant rs641738 on human liver histology with respect to steatosis and necroinflammation, and an increased prevalence of significant fibrosis [3]. The latter is the key predictor of overall mortality, liver transplantation, and liver-related events [5,6].

PIs are lipids, which regulate membrane dynamics and signal transduction pathways [4]. They consist of a glycerol backbone and two variable fatty acyl-chains, of which one is predominantly saturated and the other polyunsaturated [4]. MBOAT7 participates in acyl-chain remodeling of PIs in the Lands' cycle, in which it incorporates a polyunsaturated fatty acyl-chain into a PI [4]. In mice, knockout of *LPIAT1*, i.e. MBOAT7, affects concentrations of hepatic polyunsaturated PIs [7]. Another enzyme of the MBOAT family, *MBOAT5*, participates in the acyl-chain remodeling of phosphatidylcholines [8]. Knockout of *MBOAT5* in mice decreases arachidonic acid-containing phosphatidylcholines in the liver and increases the risk of hepatic steatosis and inflammation [8]. MBOAT7 deficiency is thus predicted to increase free polyunsaturated fatty acids [9] and their proinflammatory metabolites, which are increased in plasma of subjects with non-alcoholic steatohepatitis [10]. Detailed understanding of the mechanisms via which the altered hepatic phosphatidylinositol metabolism leads to liver fibrosis are thus of considerable interest.

In conclusion, we confirm that the common variant in *MBOAT7* rs641738 associates with histologic liver damage, particularly significant fibrosis. We extend previous data by showing that altered polyunsaturated PI metabolism characterizes the human liver in carriers of the MBOAT7 variant. These data are consistent with recent data in plasma and a role for MBOAT7 in hepatic phosphatidylinositol remodeling [3].

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Letter to the Editor

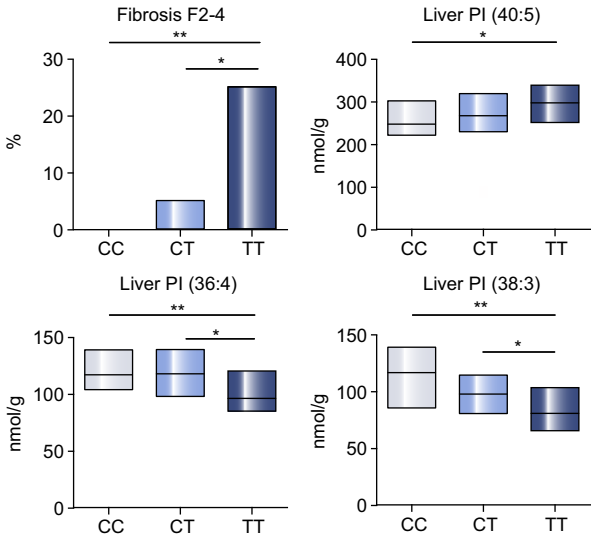

Fig. 1. Prevalence of significant fibrosis and hepatic concentrations of phosphatidylinositols PI (40:5), PI (36:4), and PI (38:3) in groups according to the *MBOAT7* genotype at rs641738. Data are in % and median (25th–75th percentile), and were tested using Pearson's χ^2 test, Kolmogorov-Smirnov test and Mann-Whitney *U* test, as appropriate. $^{*}p$ <0.05, $^{**}p$ <0.01.

Authors' contributions

PL – study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis. YZ, TH, ML, JA, MOM, MO – acquisition of data; critical revision of the manuscript for important intellectual content. HY – study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; obtained funding; study supervision.

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