MARC1 variant rs2642438 increases hepatic phosphatidylcholines and decreases severity of non-alcoholic fatty liver disease in humans

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Letter to the Editor

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MARC1 variant rs2642438 increases hepatic phosphatidylcholines and decreases severity of non-alcoholic fatty liver disease in humans

To the Editor:

We read with great interest the review by Trépo and Valenti on recent developments in genetics of NAFLD,[1] which highlighted the need for further confirmation of the association between the rs2642438 (p.A165T) variant in the mitochondrial amidoxime reducing component 1 (*MARC1*) gene and liver disease risk. This missense variant was recently shown to associate with protection from all-cause cirrhosis.[2] *MARC1* encodes for a molybdenum-containing enzyme in the outer mitochondrial membrane, which has reductive activity for N-hydroxylated compounds, *e.g.* conversion of nitrite to nitric oxide, particularly under acidic and hypoxic conditions.[3] However, the rs2642438 variant may not affect the N-reductive activity of MARC1 protein,[4] and its physiological function in NAFLD remains unclear.

Here, we examined the association of the MARC1 variant with liver histology as assessed using the SAF score (scoring of steatosis (S), activity (A), and fibrosis (F))[5] in 160 obese carriers and 209 non-carriers of the variant allele ('GA/AA' *vs.* 'GG'). The groups were similar with respect to age (49 ± 1 *vs.* 49 ± 1 years, carriers *vs.* non-carriers), gender (77% *vs.* 66% women), BMI (42 ± 1 *vs.* 42 ± 1 kg/m^2), HOMA-IR (3.7 ± 0.2 *vs.* 4.2 ± 0.3) and *PNPLA3*, *TM6SF2*, *MBOAT7* and *HSD17B13* genotypes (data not shown) (all p >0.05). Carriers had markedly lower prevalence of lobular inflammation (7.2 *vs.* 17.5 %, p = 0.006), activity (10.6 *vs.* 19.0 %, p = 0.03) and significant (F2-4) fibrosis (4.4 *vs.* 11.5 %, p = 0.01) and lower SAF score (1.5 ± 0.1 *vs.* 1.9 ± 0.1, p = 0.04) than non-carriers, while prevalence of steatosis (60.0 *vs.* 63.3%, p = 0.58) and ballooning (7.9 *vs.* 11.6 %, p = 0.28) were comparable between the groups (Fig. 1). Thus, we confirm that the *MARC1* variant rs2642438 associates with decreased severity of NAFLD.

We also assessed the association of the variant with hepatic lipid composition by ultra-high-performance liquid chromatography-

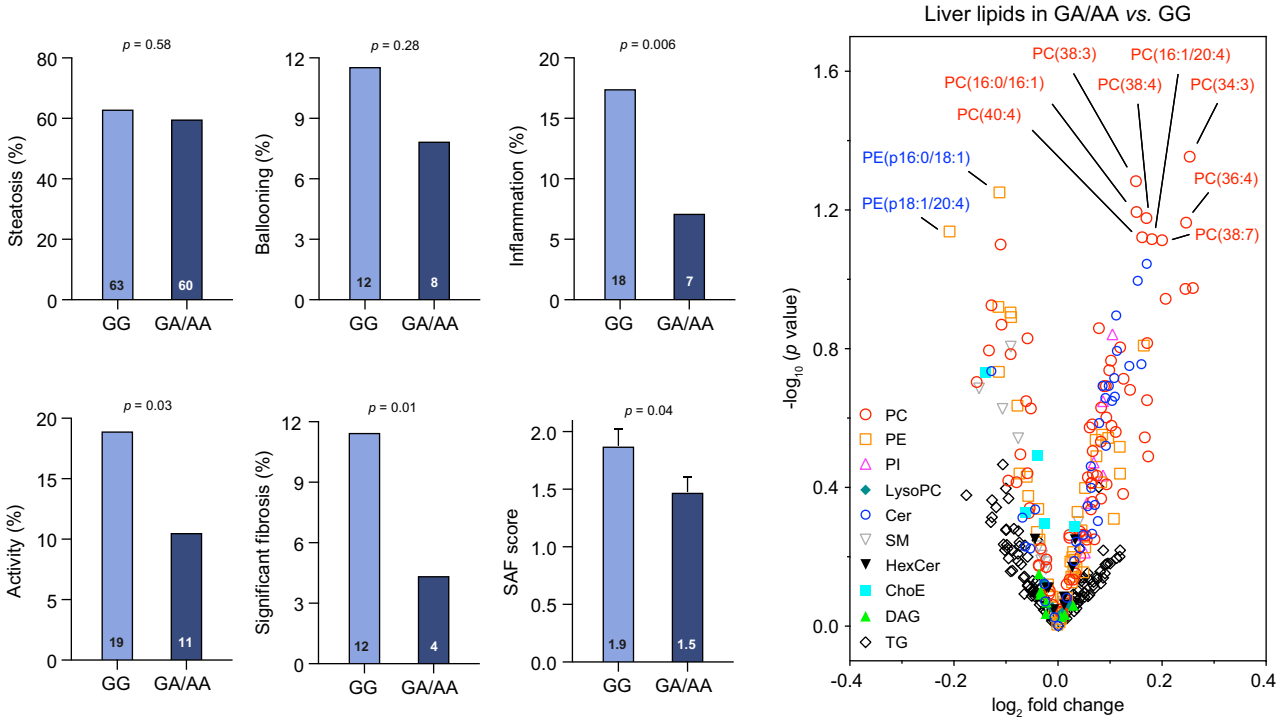

Fig. 1. *MARC1* rs2642438 associates with decreased severity of NAFLD and increased hepatic phosphatidylcholines. Bar plots show the proportion (%) of subjects with steatosis, ballooning, lobular inflammation, activity and significant fibrosis (F2-4), and total SAF score (mean ± SEM) in carriers ('GA/AA') and non-carriers ('GG') of the variant allele. Volcano plot shows differences in liver lipid composition in carriers ('GA/AA') compared to non-carriers ('GG'). Significances were determined by using Pearson's χ^2 test for categorical variables and unpaired Student's t test for continuous variables. Cer, ceramide; ChoE, cholesteryl ester; DAG, diacylglycerol; HexCer, hexosylceramide; LysoPC, lysophosphatidylcholine; NAFLD, non-alcoholic fatty liver disease; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; SM, sphingomyelin; TG, triglyceride.

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mass spectrometry[6] in a subgroup of 53 carriers and 65 non-carriers who differed similarly with respect to histology as in the entire cohort (data not shown). Carriers had higher concentrations of hepatic polyunsaturated phosphatidylcholines compared to non-carriers (Fig. 1). This hepatic lipid profile was remarkably similar to that in carriers of another recently discovered liver-protective variant, *HSD17B13* rs72613567,[7] and geometrically opposite to that in carriers of the harmful *PNPLA3* rs738409 variant.[8] These findings together with mechanistic studies in animals[9] suggest that hepatic phosphatidylcholines might play an important role in progression of NAFLD.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

PKL designed the study, analyzed data and drafted the manuscript. AJ, HS, AKP, MO, TH, JA, MO-M acquired data. HY-J designed and supervised the study. All authors critically revised the manuscript and approved the final version.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.021.

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Author names in bold designate shared co-first authorship

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