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Letters to the Editor

Reply to: HCC and liver disease risk in homozygous PNPLA3 p.I148M carriers approach monogenic inheritance

To the Editor:

We read with interest the thought-provoking letter from Krawczyk et al. [1] in response to our recent publication in the Journal of Hepatology describing the strong genetic association between the PNPLA3 rs738409 (C>G, p.I148M) variant and the development of NAFLD-associated hepatocellular carcinoma (HCC) [2]. We agree that the observed magnitude of effect is striking: comparison of genotype frequencies between a NAFLD-HCC patient cohort and an unselected UK general population sample (the MRC/Wellcome Trust UK 1958 Birth Cohort) demonstrated a 12-fold increased risk of HCC [OR 12.19; 95% CI 6.89–21.58; p < 0.0001] for rs738409 minor (G) allele homozygotes relative to C-allele homozygotes [2]. Krawczyk et al. compare the effect of PNPLA3 to the monogenic condition, hereditary haemochromatosis due to HFE rs1800562 (A>G, p.C282Y). As their detailed comparison demonstrates, carriage of either variant confers a similar risk of HCC [1].

Although statistical techniques to assess proportion of variability explained by genetic variations are imperfect [3], our data indicates a Population Attributable Risk (PAR) of PNPLA3 rs738409 for HCC of 55% and an AUROC of 0.68 attributable to this variant [2]. Further supporting the independent role of PNPLA3 rs738409 as a risk factor for HCC, it is telling that other genetic variants that are strong modifiers of NAFLD severity and fibrosis progression such as TM6SF2 [4,5], do not appear to confer an additional, independent increased risk of HCC [4]. We agree with Krawczyk et al. that PNPLA3 is an important genetic risk factor for liver disease. For the moment, we would however caution against a move towards considering “PNPLA3-associated NAFLD”, or by extension “PNPLA3-associated HCC”, as distinct, monogenic conditions analogous to HFE in haemochromatosis but rather suggest that PNPLA3 should be considered a strong modifier within a complex, polygenic disease trait that is subject both to genetic and substantial environmental influence (e.g. due to dietary factors and the intestinal microbiota [6]).

Given the mounting evidence of an association between PNPLA3 and HCC [7,8], it is timely to consider the clinical utility of PNPLA3 genotyping to assist in patient risk stratification. It has been suggested that, assuming a sensitivity of 80%, an odds ratio of >50 is required to control false-positive rates to an acceptable level of <10% [9]. A re-analysis of the data from Liu et al. [2] to assess sensitivity/specificity is shown in Table 1. Based on these data, the use of PNPLA3 genotyping alone to positively predict risk of HCC is unlikely to be tenable. However, even in this HCC-enriched dataset, the negative predictive value was substantially greater, both within the NAFLD vs. NAFLD-HCC comparison and the NAFLD-HCC vs. unselected background population comparison, and so it may be that knowledge of PNPLA3 rs738409 genotype has utility to select out those individuals least likely to develop HCC and therefore least likely to benefit from surveillance. As Krawczyk et al. suggest, studies addressing the interaction between PNPLA3 and HFE in determining HCC risk would be of great interest. Given the increasing prevalence of NAFLD-HCC and consequent clinical need for improved risk-stratification care pathways [10], we would also suggest that large, prospective studies are needed urgently to validate our findings and to determine the utility and health-economic merits of a multi-factorial risk stratification that incorporates PNPLA3 rs738409 genotype along with other recognised risk factors for HCC.

Conflict of interest

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

References


Table 1. Reanalysis of the data from Liu et al. [2] focusing on clinical utility of PNPLA3 genotype testing in HCC risk prediction.

<table>
<thead>
<tr>
<th>Cohorts (n)</th>
<th>Genotype comparison</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV*</th>
<th>NPV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAFLD-HCC (100) vs. NAFLD cohort (275)</td>
<td>GG vs. CC</td>
<td>51%</td>
<td>79%</td>
<td>47%</td>
<td>82%</td>
</tr>
<tr>
<td>NAFLD-HCC (100) vs. background UK Pop* (1476)</td>
<td>GG vs. CC</td>
<td>51%</td>
<td>92%</td>
<td>28%</td>
<td>97%</td>
</tr>
</tbody>
</table>

CI, confidence interval; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; N, number; OR, odds ratio; p, protein. Risk allele frequencies according to http://www.ncbi.nlm.nih.gov/snp/.

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Chronic kidney disease (CKD) and NAFLD: Time for awareness and screening

To the Editor:

We read with interest the article by Allen et al. reporting on the high prevalence and associated mortality of chronic kidney disease (CKD), in patients who had undergone liver transplantation [1]. We believe a thorough interpretation of these findings, which are consistent with recent liver transplant literature, should take into account the evolving aetiological spectrum of liver disease in both patients candidate for liver transplantation as well as in those with milder stage disease [2]: in either case, non-alcoholic steatohepatitis (NASH) is as an emerging risk factor for renal dysfunction, as compared with other aetiologies of cirrhosis. An analysis of the United Network Organ Sharing (UNOS) database, during the years 2002–2011, shows NASH-related cirrhosis as an increasing indication for simultaneous liver-kidney transplantation (SLKT) [3]. A concerning observation was the reduced 5-year liver graft, kidney graft, and patient survival in NASH patients in comparison to transplantation for other causes of cirrhosis (HR of 2.50 (95% CI 1.10–5.80), 2.30 (1.10–5.10), and 2.20 (1.02–5.79) respectively), for loss of liver transplant, loss of kidney graft, and death. These findings are consistent with European data suggesting NASH as a risk factor for severe renal impairment after liver transplantation; Houlihan et al. [4] reported more rapid loss of renal function in patients receiving a liver transplant for NASH-related cirrhosis in comparison to other aetiologies of cirrhosis [5]. An association of NAFLD with CKD, goes unrecognized, and in the Third National Health and Nutrition Examination Survey (NHANES III), among all individuals with moderately increasing rate of proteinuria [6], CKD often goes unrecognized, and in the Third National Health and Nutrition Survey (NHANES III), among all individuals with moderately decreased GFR (stage 3 CKD), the awareness approached 8.2% [7]. Since current therapeutic options to reverse CKD in liver transplant recipients are limited, the findings discussed above emphasize the need for practicing hepatologists to recognize early CKD in chronic liver disease patients and in NAFLD in particular, to optimize the management of these patients by delaying renal disease progression. From a therapeutical stand-point, promising preliminary evidence from randomized trials suggest several available pharmacological classes provide incremental benefits on renal disease progression over others, with statins [8] and angiotensin receptor blockers slowing renal function decline and ameliorating proteinuria [9], in addition to the...