CARRIAGE OF RS738409 IN PNPLA3 IS POSITIVELY ASSOCIATED WITH THE SEVERITY OF HISTOLOGICAL DAMAGE IN PATIENTS WITH ALCOHOLIC HEPATITIS

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Introduction and Aim:

Carriage of rs738409:G in PNPLA3 plays an important role in determining the risk for developing alcohol-related cirrhosis and influences several important aspects of disease progression and outcome. In patients with severe alcoholic hepatitis homozygosity for rs738409:G in PNPLA3 confers significant additional risk of mortality. The aim of this study was to determine whether carriage of rs738409:G is associated with the histological severity of alcoholic hepatitis at presentation.

Material and Methods:

The study population comprised participants in the Steroids or Pentoxifylline for Severe Alcoholic Hepatitis (STOPAH) trial with available DNA in whom liver histology of sufficient quality and adequately timed with respect to the start of treatment was available. The liver biopsy material was assessed by two histopathologists using the alcoholic hepatitis histological scoring system. Images were also digitally scanned and the collagen (CPA) and fat proportionate areas (FPA) quantified. Baseline, pretreatment serum levels of the M30 and M65 subtypes of cytokeratin-18 were measured by ELISA. Associations with the rs738409 genotype were examined.

Results:

A total of 129 participants (men: 89 [69%]; mean age: 49 [IQR 42 – 56]) were included, median time to biopsy was 4 days from treatment start. There was a significant positive association between carriage of rs738409:G and severe hepatic inflammation (CC: 4/53 (7.5%); CG 16/50 (32%); 4/12 (33%), $p = 0.003$) but not severe hepatocyte ballooning (CC: 29/53 (55%), CG: 31/50 (62%), GG: 5/12 (42%), $p = 0.43$). Severe inflammation and ballooning were significantly positively associated with serum levels of both CK18- M30 ($p < 0.01$) and CK18-M65 ($p < 0.01$). Carriage of rs738409:G was associated with higher serum levels of both CK18- M30 ($p = 0.01$) and CK18-M65 ($p = 0.07$). Carriage of this risk allele was associated with greater CPA (CC: 30% [22–36%], CG: 33%[24–38%], GG: 42%[29–48%], $p = 0.01$) but lower FPA [CC: 13.6% [10.0–21.5%], CG: 11.5% [8.0–17.5%], GG:8.5% [6.4–- 14.1%], $p = 0.02$).

Conclusions:

In patients presenting with alcoholic hepatitis carriage of rs738409:G in PNPLA3 is associated with more extensive hepatic fibrosis, more severe hepatic inflammation and increased serum markers of hepatocyte death. These findings may explain, in part, the higher medium-term mortality seen in carriers of this risk allele.