OWE-016 GENETIC VARIANTS IN PNPLA3 AND TM6SF2 PREDISPOSE TO HEPATOCELLULAR CARCINOMA IN PATIENTS WITH ALCOHOL-RELATED CIRRHOSIS

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Introduction Variants in patatin-like phospholipase domain-containing 3 (*PNPLA3;* rs738409), transmembrane 6 superfamily member 2 (*TM6SF2;* rs58542926) and membrane bound O-acyltransferase domain containing 7 (*MBOAT7;* rs641738) are risk factors for the development of alcohol-related cirrhosis. *PNPLA3* rs738409 is also an established risk factor for the development of hepatocellular carcinoma (HCC) within this population. The aim of this study was to explore possible risk associations of *TM6SF2* rs58542926 and *MBOAT7* rs641738 and the development of HCC.

Methods Risk variants in *PNPLA3, TM6SF2* and *MBOAT7* were genotyped in 751 cases with alcohol-related cirrhosis and HCC and in 1165 controls with alcohol-related cirrhosis without HCC. Association with the risk of developing HCC was analysed using multivariate logistic regression.

Results The development of HCC was independently associated with *PNPLA3* rs738409 (OR 1.84 [95% CI 1.55–2.18], $p=1.85\times10^{-12}$) and *TM6SF2* rs58542926 (OR 1.66 [1.30–2.13], $p=5.13\times10^{-05}$) using an additive model and after controlling for sex, age, body mass index and type 2 diabetes mellitus; the risk associated with carriage of *MBOAT7* rs641738 (OR 1.04 [0.88–1.24], p=0.61) was not significant. The population-attributable fractions were 43.5% for *PNPLA3* rs738409, 11.5% for *TM6SF2* rs58542926, and 49.9% for carriage of both variants combined.

Conclusions Carriage of *TM6SF2* rs58542926 is an additional risk factor for the development of HCC in people with alcohol–related cirrhosis. Carriage of both *PNPLA3* rs738409 and *TM6SF2* rs58542926 accounts for half of the attributable risk for HCC in this population. Genotyping will allow for more precise HCC risk stratification of patients with alcohol-related cirrhosis, and genotype-guided screening algorithms would optimise patient care.