

M64. GENOME-WIDE ASSOCIATION ANALYSES REVEAL SNP-BY-CONSUMPTION INTERACTION EFFECTS ON ALT AND AST LEVELS IN ALCOHOL DEPENDENT PATIENTS

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Background Heavy alcohol use is causally associated with liver dysfunction. Prior genome wide association studies (GWAS) identified single nucleotide polymorphisms (SNPs) associated with liver cirrhosis or elevation of liver enzymes (including aspartate aminotransferase or AST and alanine aminotransferase or ALT) in alcohol dependent subjects. Yet, it is possible that effects of SNPs on liver function may depend on the extent of recent alcohol exposure, which was not investigated in these studies. To address this gap in our knowledge, we investigated SNP-by-consumption interaction effects on the levels of three liver enzymes (AST, ALT and gamma-glutamyl transferase or GGT) commonly used in clinical practice to assess liver function in alcohol dependent subjects

Methods Self-reported alcohol consumption during previous 30 days (measured by Timeline Follow back), DNA and plasma samples for measurement of AST, ALT and GGT levels were collected from 480 alcohol dependent subjects treated in community-based treatment programs. Genotyping was conducted using Illumina HumanCore array. Multivariable linear regression models were used to assess the effects of SNP-by-consumption interaction on ALT, AST and GGT levels.

Results Genome-wide significant evidence of consumption-interaction effects on AST ($p < 5E-08$) were found for several SNPs in the C15orf41/COX6CP4 region. Top association findings of consumption-interaction effects on ALT included SNPs in EXOSC10, and the KIAA0319L/ZMYM4 region ($p < 5E-07$). Among other top results ($p < 5E-06$), were several SNPs in PCNPP2, GALNT2, and PDE9A genes that appeared to impact both AST and ALT levels in the context of the reported alcohol consumption.

Discussion Genomic location of our top association findings indicates their potential involvement in the essential cellular function, which may also be relevant for alcohol-related liver damage. Specifically, EXOSC10 gene is a putative catalytic component of the RNA exosome complex involved in proper maturation of stable RNA species such as rRNA, snRNA and snoRNA as well as elimination of RNA processing by-products. Moreover, the top SNP in ALT analysis (EXOSC10 rs2258621) might be a blood eQTL for MTOR, which is a serine/threonine protein kinase, belonging to a family of kinases mediating cellular responses to stresses such as DNA damage and nutrient deprivation. Similarly, GALNT2 encodes protein involved in metabolism and O-linked glycosylation pathways, while PDE9A encodes protein involved in signal transduction by regulating the intracellular concentration of cAMP and cGMP. Replication in the independent sample as well as investigation of the functional mechanisms behind these associations needs to follow.

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