Do common genetic variants in endotoxin signaling pathway contribute to predisposition to alcoholic liver cirrhosis?

BACKGROUND: Tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta), produced by endotoxin-activated Kupffer cells, play a key role in the pathogenesis of alcoholic liver cirrhosis (ALC). Alleles TNFA -238A, IL1B -31T and variant IL1RN*2 of repeat polymorphism in the gene encoding the IL-1 receptor antagonist increase production of TNF-alpha and IL-1beta, respectively. Alleles CD14 -159T, TLR4 c.896G and TLR4 c.1196T modify activation of Kupffer cells by endotoxin. We confirmed the published associations between these common variants and genetic predisposition to ALC by means of a large case-control association study conducted on two Central European populations.

METHODS: The study population comprised a Czech sample of 198 ALC patients and 370 controls (MONICA project), and a German sample of 173 ALC patients and 331 controls (KORA-Augsburg), and 109 heavy drinkers without liver disease.

RESULTS: Single locus analysis revealed no significant difference between patients and controls in all tested loci. Diplotype [IL1RN 2/2; IL1B -31T+] was associated with increased risk of ALC in the pilot study, but not in the validation samples.

CONCLUSIONS: Although cytokine mediated immune reactions play a role in the pathogenesis of ALC, hereditary susceptibility caused
by variants in the corresponding genes is low in Central European populations.