Article: 0474
Topic: EPO10 - e-Poster Oral 10: Addictive Behaviours, Anxiety Disorders and Somatoform Disorders

Abstinence Length in Acamprosate-treated Alcoholics and Variability in Glycine and Glutamate Signaling Gene Sets

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Background

We recently identified association between *GRIN2B* rs2058878 variant and abstinence length in acamprosate-treated alcoholics (Karpyak et al. 2014). Here we present results of additional analyses exploring associations in the same sample (225 alcoholics treated with acamprosate for three months) at the gene and gene-set levels, for 12 genes involved in glycine signaling, 4 genes involved in glutamate reuptake, synthesis and degradation and 7 genes encoding NMDA receptor subunits.

Methods

After adjustment for relevant covariates, gene-level tests were performed using principal components (PC) analysis. Gene-set analyses were performed using the PC-Gamma approach with varying soft truncation threshold (STT) for the Gamma method for combining gene-level p-values.

Results

Shorter abstinence was associated with increased intensity of alcohol craving and lower number of days between last drink and initiation of acamprosate treatment. After adjustment for covariates, we observed nominally significant association of abstinence length with variation in the *AMT* (p=0.024), GRIN3A (p=0.016) and SHMT2 (p=0.039) genes, and marginally significant evidence for association with the GRIN2B (p=0.067) and GLRB (p=0.060) genes. At the gene-set level, association of abstinence length with variation in the glycine pathway was nominally significant (p=0.042 with STT=0.37). Marginal evidence of association with abstinence length was also observed for variation in the NMDA-receptor subunits ($p<0.1$ for $STT<0.15$).

Discussion

Our findings suggest association of abstinence length in acamprosate-treated alcoholics with variation in the glycine signaling pathway and genes encoding NMDA receptor subunits. Investigation of the mechanisms underlying these associations and their usefulness for individualized treatment selection should follow.

https://doi.org/10.1016/S0924-9338(15)31896-4 Published online by Cambridge University Press