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Pharmacogenomics research in substance use disorders: insights from clinical trial and brain organoids

Background:

We previously conducted an open label acamprosate trial (n=442) in patients with alcohol use disorder (AUD). Acamprosate is an FDA-approved medication for the treatment of AUD, however, only about 50% of patients will respond to acamprosate. To date, no biological measures are utilized to predict response to acamprosate treatment, and craving intensity. To address this gap, we aimed to identify potential biomarkers associated with alcohol craving intensity using multi-omics data from our acamprosate study—the largest acamprosate trial of its kind and the only one with multi-omics data.

Methods:

Primary outcomes were relapse to any alcohol use and relapse to heavy drinking, assessed using the timeline follow-back method. Baseline plasma proteins were quantified using Olink platform. Genome-wide association studies were conducted for plasma cortisol levels. Functional genomic studies were performed in patient-derived induced pluripotent stem cells (iPSCs) to explore mechanistic pathways.

Results:

Baseline craving intensity was the strongest clinical predictor of relapse ($p = 9.36 \times 10^{-6}$). Plasma levels of HSD11B1, which converts cortisone to active cortisol, were associated with both craving intensity and treatment outcomes. Baseline cortisol levels positively correlated with craving severity. Genome-wide analysis identified significant variants within the KHNYN–CBLN3 locus on chromosome 14 associated with plasma cortisol levels; notably, the same variant was linked to acamprosate response. Functional studies in patient-derived iPSCs suggest that KHNYN and CBLN3 may influence cortisol metabolism and interferon signaling pathways.

Conclusions:

This integrative multi-omics approach identifies potential biomarkers and biological mechanisms underlying acamprosate response. These findings advance understanding of AUD pathophysiology and may inform development of novel anti-craving therapeutic strategies.

Authors:

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