Article: EPA-0871
Topic: FC09 - Free Communications Session 09: Genetics and molecular neurobiology

GENOME-WIDE ASSOCIATION STUDY OF NMDA RECEPTOR COAGONISTS IN CEREBROSPINAL FLUID AND PLASMA IDENTIFIES METABOLIC AND TRANSPORTER PATHWAYS

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The N-methyl-D-aspartate receptor (NMDAR) co-agonists Glycine, D-Serine, L-Proline and possibly D-Alanine play crucial roles in NMDAR-dependent neurotransmission and were shown to mediate susceptibility to neuropsychiatric disorders. Cerebrospinal fluid (CSF) has not been targeted in genome-wide associations studies (GWASs) of NMDAR co-agonists. Moreover, mechanisms underlying amino acid enantiomer concentration variations remain elusive although heritability estimates suggest amino acids in other body fluid compartments are under genetic control.

We conducted GWASs of Proline, Serine, Glycine and Alanine enantiomer concentrations (and ratios) in the plasma and cerebrospinal fluid (CSF) of healthy human subjects (N=414).

A number of metabolic QTLs were identified. Variants on 22q11.2, located 35kb from *PRODH*, were associated with L-Proline in plasma (standardized $\beta = 0.29$; $P = 6.38 \times 10^{-10}$). The missense variant rs17279437 in the Proline transporter *SLC6A20* associated with both L-Proline in CSF ($\beta = 0.28$; $P = 9.68 \times 10^{-9}$) and the L-Proline plasma-CSF ratio ($\beta = -0.30$; $P = 2.88 \times 10^{-9}$). Suggestively significant association was found for the D-serine plasma-CSF ratio at the D-amino-acid oxidase (*DAO*) gene ($\beta = -0.28$; $P = 9.08 \times 10^{-8}$).

These metabolic QTL findings portend substantial power of GWASs targeting CSF constituents in neurologically healthy human subjects. We demonstrate how L and D-enantiomer quantitative analyses deepen the understanding of NMDAR co-agonist metabolic and transporter mechanisms. The detected L-Proline QTLs on chromosome 22q11 and 3p21.31 potentially set a stage for further genetic and pharmacological studies in patients suffering 22q11 deletion syndrome and hyperprolinemia.

https://doi.org/10.1016/S0924-9338(14)78202-1 Published online by Cambridge University Press