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TITLE: Integrative Multi-Omics Analysis of Epigenomic and Metabolomic data for Attention-Deficit/Hyperactivity Disorder

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KEYWORDS: multi-omics, attention-deficit/hyperactivity disorder, epigenomics, metabolomics, twins

ABSTRACT:

Attention-deficit/hyperactivity disorder (ADHD) is a complex trait with a substantial

heritability with other ‘omics’ e.g. epigenomics and metabolomics, influences on ADHD beginning to be explored. Multi-omics is an evolving field which combines data from multiple ‘omics’ levels and provides methods for their simultaneous analyses to identify biological mechanisms and biomarkers for complex traits. This project applies an integrative multi-omics method, called DIABLO, based on multi-block Partial Least Squares Discriminant Analysis (PLS-DA) to build a predictive model for ADHD from metabolomics and epigenomics data.

First-morning urine and buccal-cell samples were collected from 606 twins (N complete pairs = 275, mean age = 9.3 [SD=0.63], male = 54.9%) who took part in Netherlands Twin Register ACTION project (Aggression in Children: Unraveling gene-environment interplay to inform Treatment and InterventiON strategies).

Dichotomous ADHD status was based on the mother-rated Revised Conners’ Parent Rating Scale (CPRS-R). First, in 20% of the data, the discriminative capacities of each ‘omics’ level and pair-wise cross-omics relationships were analysed with PLS-DA and PLS, respectively. Next, multi-block PLS-DA was applied to 50% of the data. The resulting model was used to predict the ADHD status in the remaining 30% of the data. The model selected metabolites and methylation probes involved in dopaminergic pathways and oxidative stress, mechanisms that have previously been associated with ADHD. However, the predictive accuracy of the model was relatively low (Area under the curve = 0.449-0.588  $p > 0.10$ ). Overall, the model seems promising and underlines the potential of a multi-omics approach in complex traits such as ADHD.

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