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A meta-analysis of epigenome-wide studies across the lifespan

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ABSTRACT:

Here we report an EWAS meta-analysis (EWAMA) of broadly defined aggressive behavior in peripheral blood samples for 14,434 participants from 18 cohorts with mean ages ranging from 7 to 68 years, and cord blood samples for 2,425 children from 5 cohorts with aggression assessed at ages ranging from 4 to 7 years. In an additional group of 1235 9-year old children and 172 children enrolled in a childhood psychiatric clinic, buccal cell-derived DNA methylation profiles were available.

In blood samples, 13 methylation sites were significantly associated with aggression after Bonferroni correction. No epigenome-wide significant sites were found in cord blood samples, but 83% of these sites showed the same direction of association in cord blood with aggression in childhood ($r=0.74$, $p=0.006$). Regression coefficients based on analyses in buccal cells and blood overall showed no directional consistency.

Top-sites ($FDR<0.05$) from the analysis of blood samples in children and adults were previously reported for association with chemical exposures, smoking, cognition, metabolic traits, and mQTLs. Three genes whose expression levels were associated with top-sites were previously linked to schizophrenia and general risk tolerance, pointing to loci that are correlated with substance use and chemical exposures, as well as genetic variation. At some loci, DNA methylation variation in blood mirrors variation in the brain.

Epigenetic profiles may capture lifetime cumulative effects of genetic, stochastic, and environmental influences associated with aggression. Our findings may serve as potential biomarkers and possibly indicate causal relationships with aggression and form a basis for future projects.

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