Attention Deficit/Hyperactivity Disorder (ADHD) has been demonstrated to be highly heritable, but so far molecular genetic studies have explained only a small percentage of the heritability. Here, we consider the role of epigenetics – specifically examining gene methylation – in the etiopathology of longitudinally-persistent attention problems (AP), a quantitative phenotype related to ADHD.

Subjects were fifty monozygotic (MZ) twin pairs selected from the Netherlands Twin Registry and for whom longitudinal information was available on attention problems. 22 concordant affected (CA), 17 concordant unaffected (CU), and 11 discordant pairs participated. Whole genome methylation scans failed in 2 of the CU twins, resulting in a final sample size of 48.

The Child Behavior Checklist (CBCL) Attention Problems (AP) scale was completed by parents at ages 7, 10 and 12. Individuals were selected as affected if they had a T-score > 65 for AP on at least one occasion and a T-score > 60 for AP at all three time points.

Environmental Effects:
156 promoter methylation sites were significantly different between the discordant twins. Three canonical pathways were significant following adjustment for multiple comparisons, IL-6 signaling (4 molecules, p<0.03), G-protein coupled receptor signaling (5 molecules, p<0.03), and relaxin signaling (5 molecules, p<0.03). The calcyon neuron-specific vesicular protein (CALY) stood out as significant (p=7.45 x 10^{-5}).

Genetic Effects:
359 promoter methylation sites were significantly different between the CA pairs and the CU pairs. The neuregulin signaling canonical pathway came very near to significance following adjustment for multiple comparisons (6 molecules, p = 0.0537). The GDNF family receptor alpha 1 (GFRA1) stood out as significant (p=2.68 x 10^{-5}).

This is the first study of differential methylation in attention problems using twins. There may be separate mechanisms for “genetic” methylation pathways and “environmental” methylation pathways.