

## **Loneliness and DNA methylation of variants in the conserved transcriptional response to adversity (CTRA) pathway**

Dianna Phillips, University of California Riverside; Yunzhang Wang, Nancy L Pedersen, and Sara Hägg, Karolinska Institutet; Chandra Reynolds, University of California Riverside

Loneliness predicts a variety of adverse outcomes related to physical, mental, and cognitive health and is potentially modifiable. Although mechanisms behind these associations remain to be elucidated, prior work suggests that persons who are chronically lonely have altered expression of genes in blood leukocytes related to inflammation and immune processes referred to as a conserved transcriptional response to adversity (CTRA).

We explored the association between loneliness and methylation at 1586 CpG sites (measured from whole blood using the Illumina HumanMethylation450 array) associated with 105 CTRA genes by fitting Bayesian mixed-effects growth models to longitudinal methylation data from 386 twins (60.1% female, 48–94 years, Mage = 68.66, SD = 9.22) from the Swedish Adoption Twin Study of Aging (SATSA), adjusting for age and sex. 82 CpGs from 50 CTRA genes showed nominal significance ( $p < 0.05$ ) for effects of time-varying loneliness on methylation level or change, including multiple CpGs in SLC12A7, EP400, HNRPL, TOP2B, STAT1, PTPN12, IGFBP3, and COL6A2. Notably, among CpGs most strongly associated with change ( $p < 0.0027$ ), age-associated methylation increases were observed among those who felt lonely for sites in CPT1B, SMARCC1, and TOP2B. No effects were significant after correcting for multiple testing. We evaluated causality versus confounding of observed associations considering baseline loneliness and longitudinal methylation, observing within-pair effects of increased methylation for the lonelier twin for the TOP2B site (cg19472303), that was reduced for MZ versus DZ pairs. Altogether, the effects of loneliness on longitudinal methylation, while modest, suggest possible sensitivity to experiences of perceived loneliness.