

Title: Grandpaternal BMI in youth associates with DNA methylation of paternal grandchildren

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Abstract

Pre-pubertal food availability has been shown to associate with paternal grandson mortality, commonly regarded as an example of transgenerational inheritance in humans, which could potentially be mediated by epigenetic mechanisms. We aim to investigate whether grandpaternal BMI in youth associates with the DNA methylation profile of their adult grandchildren.

We used genome-wide blood DNA methylation data from the Young Finns Study (YFS) and obtained the BMI of their grandfathers from military records compiled in drafts (aged 18–20y). Epigenome-wide association studies were performed for all grandchildren (34–49y; $n=504$) and separately for paternal grandchildren ($n=337$), paternal grandsons ($n=147$), maternal grandchildren ($n=331$) and maternal granddaughters ($n=159$). Models were adjusted with the soldier's occupation, Eastern or Western Finnish origins, age at drafting as well as the grandchildren's own BMI, age, sex and smoking status, in addition to methylation-based estimates of cell proportions and principal components of methylation technical probes.

Significant associations ($p_{FDR}<0.05$) were identified for 15 loci for all grandchildren and in the paternal line (63 loci for paternal grandchildren and 24 loci for paternal grandsons). No significant associations were identified in the maternal line. Interestingly, 9 of the identified loci locate to suggested imprinted genes, making them candidates for transgenerational transmission due to their potential to escape the wave of demethylation that occurs during embryogenesis. Further research will include replication in the soldiers' offspring and great-grandchildren as well as associations with microRNA and DNA methylation from sperm of all three generations.