Multi-phenotype epigenome-wide association analysis of fasting glucose and insulin in 981 Finnish individuals

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BACKGROUND: Multi-phenotype genome-wide association studies (MP-GWAS) of correlated traits have greater power to detect genotype–phenotype associations than single-trait GWAS. In our previously-developed MP-GWAS method, implemented in the SCOPA software, single-nucleotide polymorphism (SNP) genotype dosage is 'reversely' regressed on a linear combination of phenotypes. Considering the epidemiologic correlations between fasting plasma glucose (FG) and fasting insulin (FI) levels, we aimed to use a SCOPA adaptation for multi-phenotype epigenome-wide association analysis (MP-EWAS) for these two traits in non-diabetic individuals.

METHODS: We developed the "methylSCOPA" software, extending the SCOPA approach to MP-EWAS using DNA [hyper/hypo]methylation data, and applied it to FG, FI and Illumina Infinium HumanMethylation450K BeadChip array data from the Northern Finland Birth Cohorts (NFBC) 1966/1986. We subjected all data to stringent quality control and corrected them for measured (potential) confounders by linear regression analysis, and normalized the methylation signal intensity and FI data. The MP-EWAS included data for 635/346 individuals and 459,378/466,290 methylation probes from NFBC1966 and NFBC1986, respectively. We meta-analyzed the study-specific MP-EWAS results, mapped genomic locations to CGCh37/hg19, and adopted $p<1\times10^{-7}$ to denote epigenome-wide significance.

RESULTS: In meta-analysis, the MP-EWAS association involving a methylation marker located at chromosome 22:49,088,813 and annotated to *FAM19A5* attained the lowest *p*-value ($p=1.4\times10^{-7}$) epigenome-wide. In single-trait FG and FI EWAS meta-analyses, the associations involving this marker attained $p=0.13$ and $p=4.0\times10^{-3}$, respectively.

CONCLUSION: We extended our MP approach to MP-EWAS, and demonstrated its enhanced power over single-trait analysis for detection of MP epigenetic effects in large-scale data.

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