


# Umbilical Cord Blood DNA Methylation Loci Associated with Gestational Age at Birth

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## Introduction

DNA methylation (DNAm) is highly sensitive to in utero perturbations and has an established role in both early development and regulation of gene expression. The fetal genetic component has been shown to contribute significantly to timing of birth, yet little is known about the identity and behavior of individual genes.

## Objectives

1. Test for association between **genome-wide DNAm** levels in umbilical cord blood with **gestational age at birth**.
2. **Validate** DNAm findings in an independent sample.
3. Multi-omic approach to evaluate DNAm cis-gene relationships with **gene expression regulation**.

## Methods

- Illumina Infinium Human Methylation 450K BeadChip:
  - Pregnancy, Race, Environment, Genes Study (**PREG** - VCU) (N= 124)
  - Newborn Epigenetic SStudy (**NEST** - Duke) (N= 378)
- Consistency of differentially methylated positions (DMPs) was assessed in multiple ways:
  - Degree of overlap in cohorts was non-random by simulation study
  - Concordant in both direction of change and size of effects
- CpGs significant in both studies (FDR=5%) were tested for association with *cis*-gene expression

## Support

NIHMD (P60MD002256, PI: York, Strauss); NIEHS (R21ES014947, PI: Hoyo) and NIEHS (R01ES016772, PI: Hoyo); NIDDK (R01DK085173, PI: Hoyo).

>50% of variation in gestational age explained by umbilical cord DNAm.

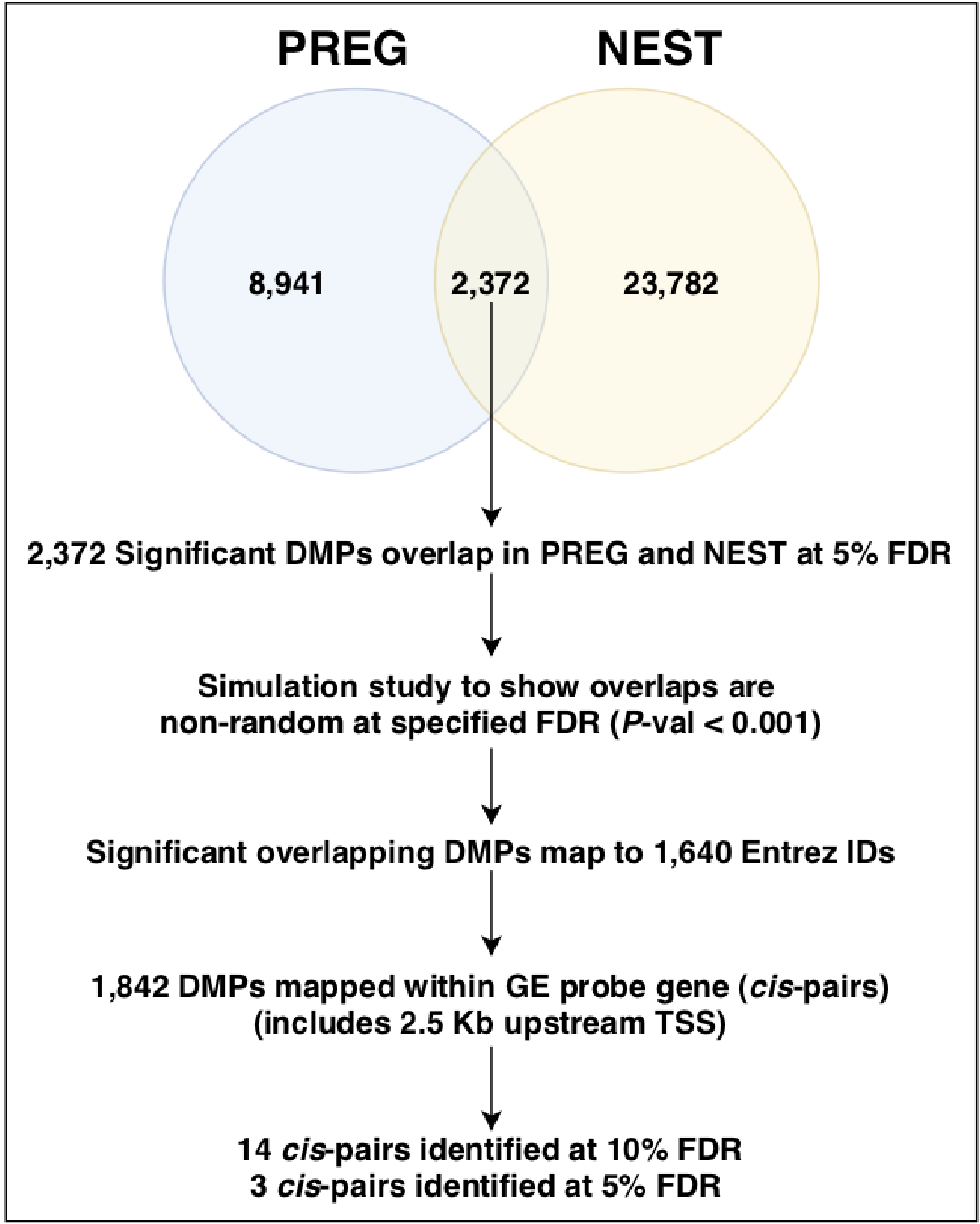
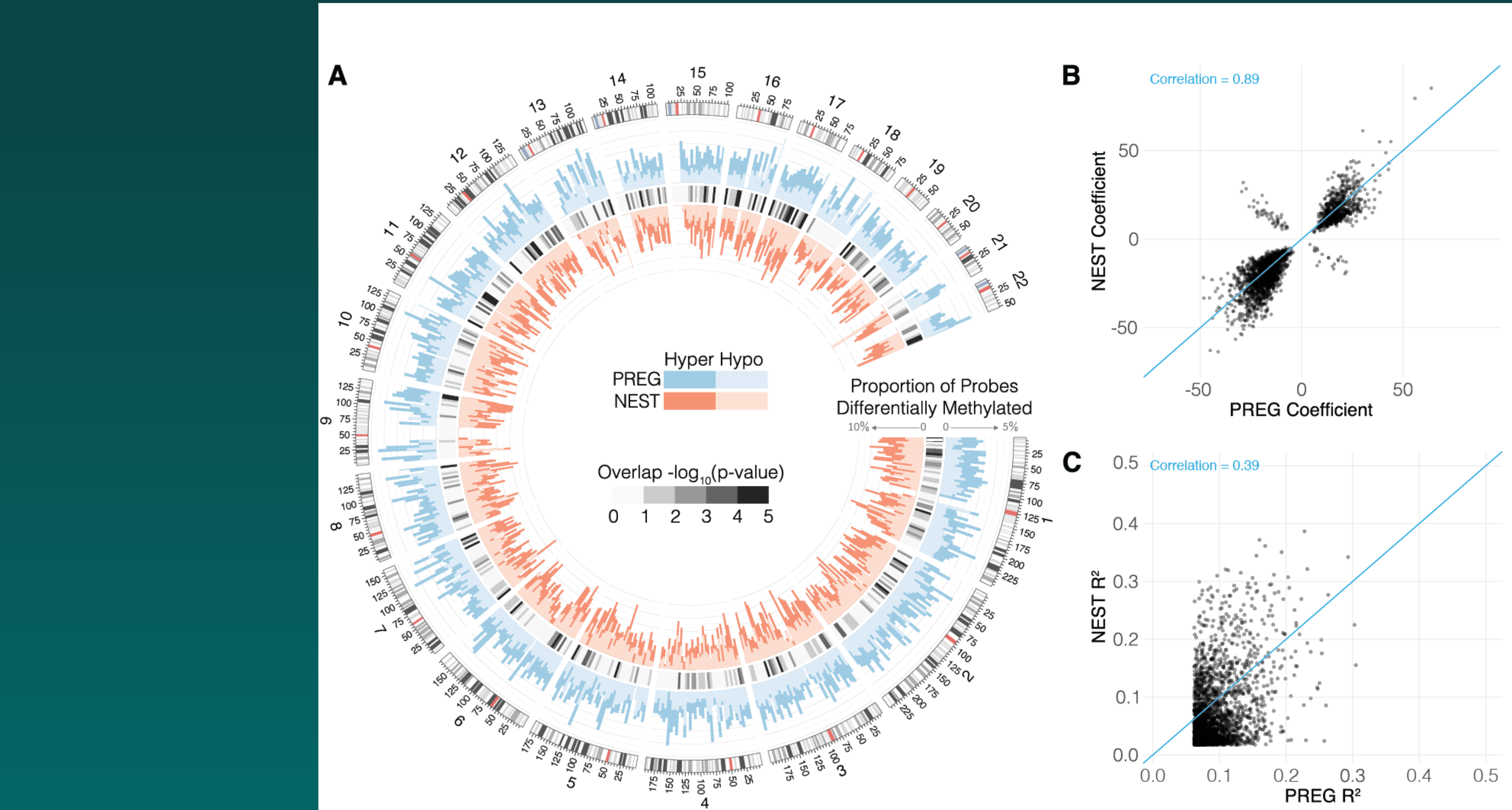


Figure 1: PREG and NEST cohort DNA methylation array probe and sample filtering summary for major processing steps.

PREG / NEST CpG and Gene Overlap							
FDR	Significant CpG		CpG Overlap	Gene Overlap <sup>1</sup>	Null CpG Overlap Estimate		
	PREG	NEST			Median	IQR	P-val <sup>2</sup>
1.00	445080	444484	444399	21316	NA	NA	NA
0.01	9647	16679	1569	1123	360.0	23.00	0
0.05	25421	29104	3964	2600	1662.5	50.25	0
0.10	45656	41083	7388	4364	4215.5	74.00	0
0.15	66943	52551	11655	6281	7902.5	107.25	0

<sup>1</sup> Both gene and promoter coverage  
<sup>2</sup> From 10K permutations

Figure 2: Simulation study of overlapping CpG results from PREG and NEST

Gene	Entrez ID	Affy Probeset	CpG Probe	Chrom.	CpG Position	Coef	P-value	R-square <sup>1</sup>	Gene Relevance
TRIM33	51592	212435.at	cg26410133	chr1	115051834	-2.309	0.001	0.156	Regulates proinflammatory function of Th17 cells [58]
CD247	919	210031.at	cg15518113	chr1	167490121	-1.124	0.000	0.395	Impaired immune response [59]
PLCH1	23007	214745.at	cg26905011	chr3	155422103	0.283	0.001	0.145	Cord blood association with PTB [60]
F2RL1	2150	213506.at	cg00499700	chr5	76116088	-1.852	0.001	0.151	Regulation of symmetrical function at labor and preterm labor [61]
KEL	3792	206077.at	cg17784922	chr7	142559425	-1.242	0.001	0.113	Anti-Kel associated with increased risk for PTB [62]
EXT1	2131	201995.at	cg20547777	chr8	119086580	0.841	0.000	0.141	Necessary for heparan sulfate elongation which enhances neutrophil infiltration [63]
EXT1	2131	214985.at	cg20547777	chr8	119086580	0.669	0.000	0.205	
EXT1	2131	201995.at	cg16005311	chr8	119086762	0.876	0.000	0.149	"
EXT1	2131	214985.at	cg16005311	chr8	119086762	0.668	0.000	0.198	"
SIGIRR	59307	218921.at	cg8809273	chr11	413594	-1.185	0.001	0.136	Negative regulation of TLR and IL-1 receptor signalling to elicit immune response [64]
CHD4	1108	201184.a.at	cg20608050	chr12	6712515	0.889	0.000	0.148	Nucleosome remodeling and deacetylase complex [65]
ART4	420	207220.at	cg20967028	chr12	14996272	-1.696	0.000	0.106	ADP-ribosyltransferase 4 (Dombrock blood group)
CTDP1	9150	205035.at	cg24908981	chr18	77441810	-0.878	0.000	0.175	CTD phosphatase subunit 1
CSF7	8530	210140.at	cg19204859	chr20	24933798	-0.875	0.000	0.159	Innate immunity by affecting cytotoxicity of NK cells [66]

Figure 3: DMP cis Gene Expression Association.

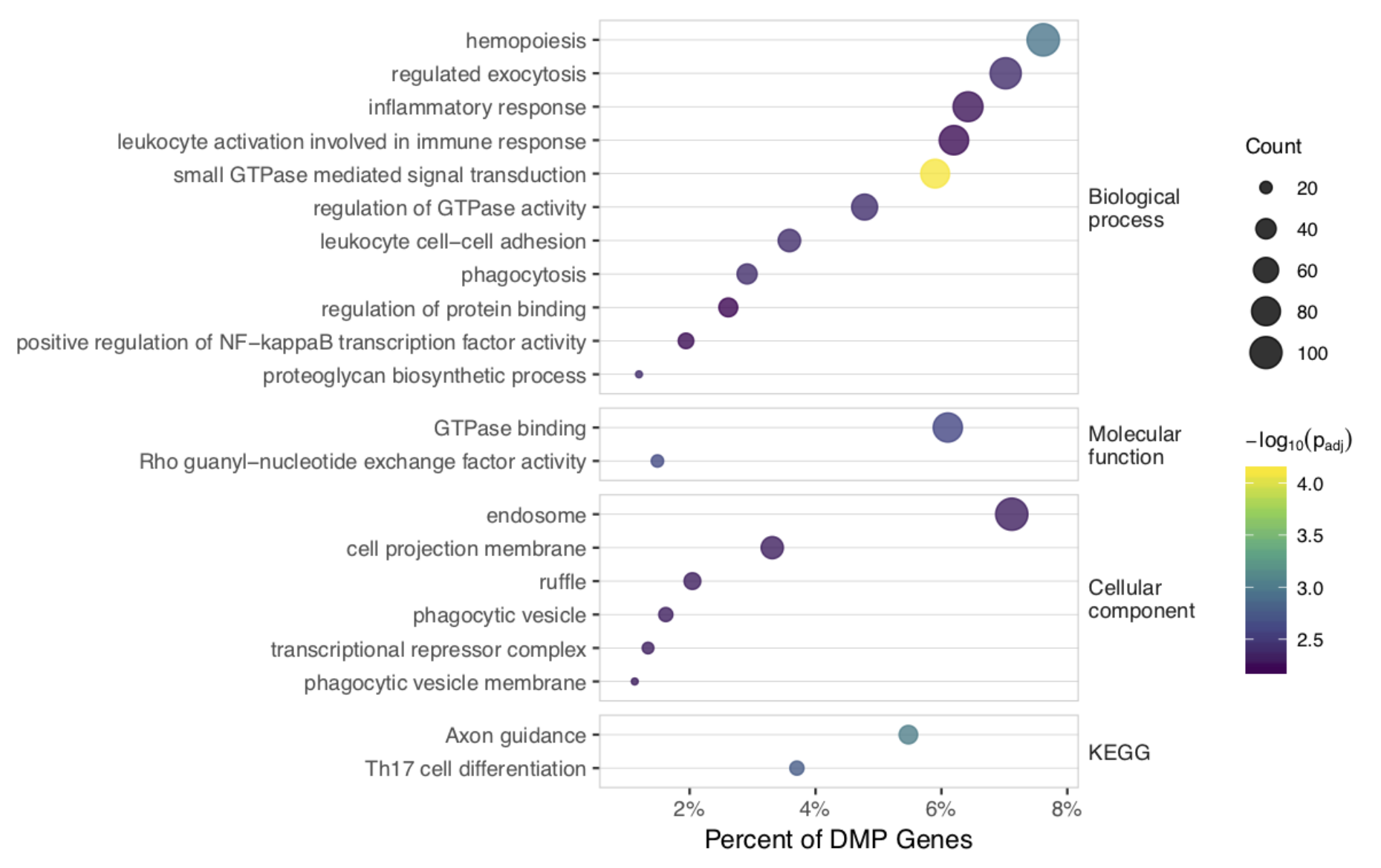


Figure 4: Gene-based enrichment for Gene Ontology groups and KEGG pathways.

