Cord Blood DNA Methylation Levels in Genes Regulating Hematopoietic and Mesenchymal Cells are Associated with Infant White Matter Microstructure

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BACKGROUND

- Maternal health and environment may initiate epigenetic modifications regulating brain architecture.
- Developing white matter (WM) is sensitive to adverse environments[1-3]; however molecular mechanisms are unknown.
- Differentially methylated neurodevelopmental genes & networks in cord blood (CB) were associated with WM microstructure related to maternal depression & anxiety[4].
- CB hematopoietic & mesenchymal cells given in neonatal encephalopathy may improve WM microstructure by yet unknown mechanisms.

Objective: Determine if CB DNA methylation levels in hematopoietic & mesenchymal genes are related to infant WM microstructure associated with prenatal maternal depression & anxiety.

METHODS

- CB collected at birth, plasma removed, DNA from packed nucleated blood cells studied.
- DNA methylation levels determined by Infinium HumanMethylationEPIC array to determine Differentially Methylated Positions (DMP).
- NODDI MRI (neurite orientation dispersion & density imaging) acquired during non-sedated sleep[5] (N=55 both CB & NODDI).
- Linear regressions between DNA methylation and v_{IC} measures (neurite density–volume fraction for intracellular restricted diffusion compartment) in areas associated with maternal depression & anxiety (Fig. 1).
  - Controlled for: CB cell numbers, sex, gestation corrected age, socioeconomic status, & motion.

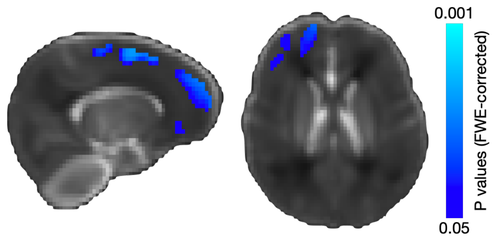


Fig. 1: Regions where v_{IC} was negatively associated with maternal depression and anxiety.

RESULTS

Fig. 2. Gene-concept network plot shows top 5 gene ontology terms (beige), genes (gray) associated with each term, & interconnectivity between genes & processes (lines). Beige dot size relates to # of DMP-associated genes contributing to term.

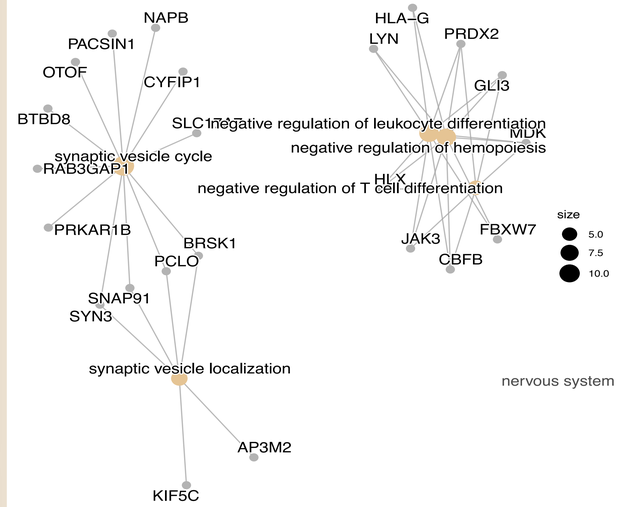


Fig. 3. Enrichment map plot depicts connectivity of associated terms, with hubs of similar processes clustering. Node size represent relative # of DMP-associated genes contributing, while color depicts FDR *p*-value, Fischer test.

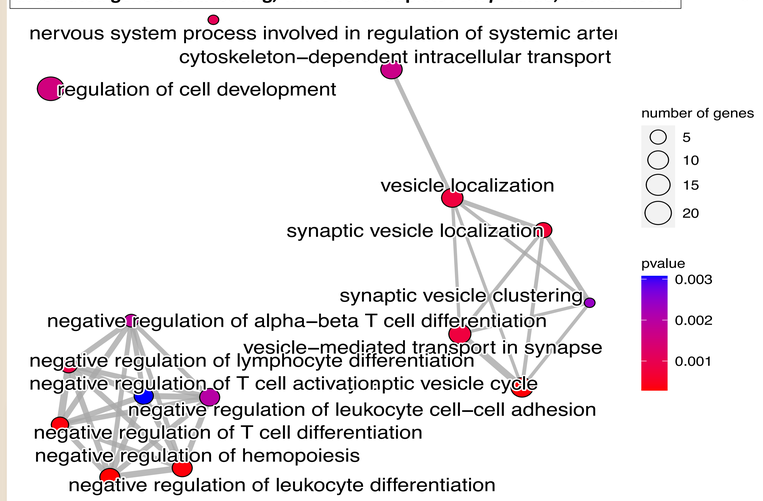
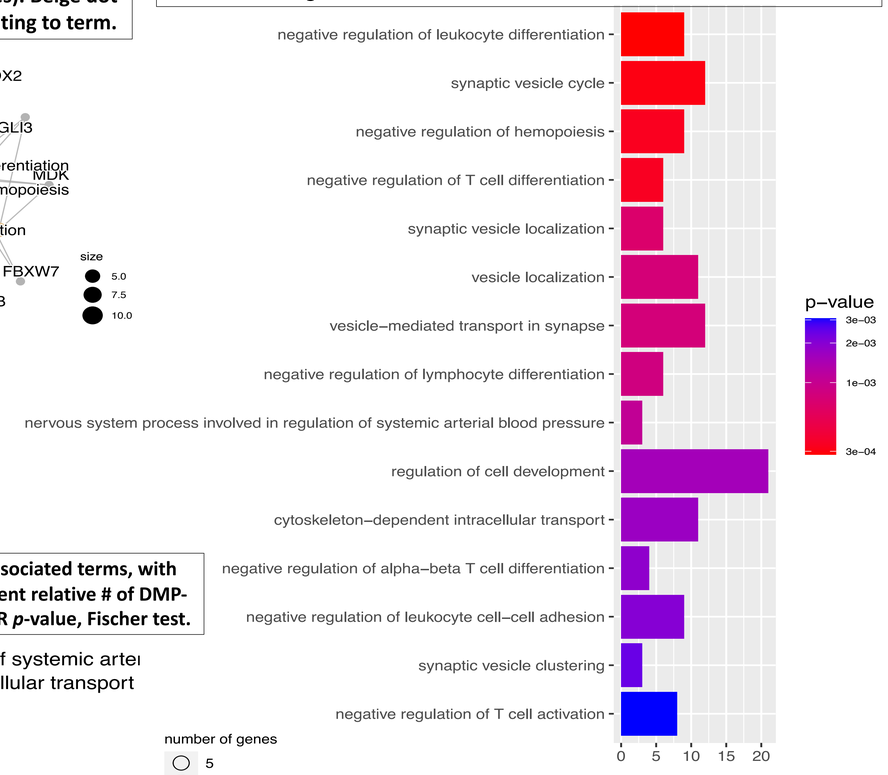


Fig. 4. Bar Graph of top gene ontological (GO) biological processes associated with DMP genes, ordered by statistical significance, with x-axis bar length indicates # of DMP-associated genes.



In addition to those in neurodevelopment, CB DNA methylation levels in hematopoietic & mesenchymal genes & networks are associated with 1-month infant NODDI neurite microstructure.

- 351 DMPs in CB were associated with infant MRI neurite density (v_{IC}) ($p<0.05$, FDR-corrected) in areas associated with maternal depression & anxiety.
- Gene ontological (GO) annotation of v_{IC}-associated DMPs revealed that 50% of top 24 significant pathways involved in negative regulation of hematopoietic & mesodermal stem cell development & function, i.e., negative regulators of inflammatory cells. Several genes include TAL1, JAK3, SMAD1, HOXA11, & FOXC1

CONCLUSIONS

- Impact of prenatal maternal depression & anxiety on neurodevelopment may act, in part, through modifying methylation & gene expression patterns that regulate hematopoietic & mesenchymal processes, in addition to neurodevelopmental processes.
- Understanding these microstructural processes helps to inform genetic & epigenetic contributions guiding early brain development.
- Future work plans to extend DNA methylation analyses to investigate genes specifically involved in regulating myelination & axonal generation, as well as associations with infant behavior.

ADDITIONAL KEY INFORMATION

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