Data Article

Genome-wide DNA methylation data from adult brain following prenatal immune activation and dietary intervention

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ABSTRACT

DNA methylation is a dynamic epigenetic mark regulating gene function and are implicated in the pathophysiology of schizophrenia and autism. Environmental exposures such as inflammation and diet modify the epigenome and may explain why prenatal exposure to inflammation increase risk of neurodevelopmental disorders. This manuscript presents genome-wide DNA methylation data (GSE102942) generated from adult offspring brain prenatally exposed to Maternal Immune Activation (MIA). Methylome of the adult brain supplemented with omega-3 polyunsaturated fatty acids (PUFA) is also described. DNA methylation across gene regulatory regions were measured using MSP-I digestion and Reduced Representation Bisulfite Sequencing (RRBS) method.

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Specifications Table

Subject area	*Neuroscience*
Specific subject area	*Psychiatric epigenetics*
Type of data	*Tables,*
	Raw sequencing data
How data was acquired	*DNA was isolated and bisulfite converted, data generated using RRBS method including high-throughput sequencing.*
Data format	*Raw*
	Analysed
Parameters for data collection	*MIA model, Bisulfite conversion, Reduced Representation Bisulfite Sequencing*
Description of data collection	*Genomic DNA was isolated, fragmented using MSP-I restriction digestion, bisulfite converted and sequenced following the RRBS protocol.*
Data source location	*Baylor College of Medicine*
	Houston, TX,
	USA
Data accessibility	*Repository name: Gene Expression Omnibus*
	Data identification number: GSE102942
	Direct URL to data: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE102942
	Secure token: wjqzkggohhwltqz
Related research article	*Basil P, Li Q, Gui H, Hui TCK, Ling VHM, Wong CCY et al. Prenatal immune activation alters the adult neural epigenome but can be partly stabilised by a n-3 polyunsaturated fatty acid diet. Translational psychiatry.*
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Value of the Data
- This dataset gives the genome-wide DNA methylation profile of adult brain exposed to prenatal immune activation and modified diet.
- Genome-wide DNA methylation of regulatory regions measured at single base pair resolution could predict genes affected by environmental exposures. Epigenetic marks in an animal model relevant to schizophrenia and autism could be tested for a biomarker for the disease.
- Dataset includes epigenetic profiles of control and n3-PUFA administered adult brain which could be used to track methylation changes in a normal and abnormal adult brain.
- Diet induced epigenome provides insights into a low-cost intervention of the modifiable epigenome in neurodevelopmental conditions.

1. Data

This manuscript describes methylome datasets generated using next-generation sequencing (NGS) from hypothalamus of offspring exposed to prenatal infection. The raw data is available at Gene Expression Omnibus database with accession number GSE102942. Data was generated from home cages considered as experimental units (prenatal inflammation group; n = 12 males; n = 6 females = 6) and matched controls (control group; n = 12 males; n = 6 females = 6). Half of the experimental units in each group received dietary intervention with n-3 PUFA from weaning. Fig. 3 shows the number of animals used in the study and the diet composition is described elsewhere [1]. Methylation data was generated using RRBS protocol [2] from 12-week (equivalent to adult) mouse brain tissue. In short, 2.5 μg of genomic DNA was digested using MSP-I restriction enzyme incubating for overnight at 37 °C. Fragments of size within 150–470 were purified on a 2% agarose gel, library was produced using Illumina TruSeq DNA kit and sequenced in an Illumina HiSeq 2000 system.

Raw sequencing data for 24 samples labeled as Saline (control group) or PolyI:C (MIA group) and n-6 (normal diet) or n-3 (modified diet) are provided as Sequence Read Archives. Please see Fig. 1 for data quality analysis results. Processed files are provided as DNA methylation values, measured as C/T ratios compared between 1. PolyI:C group against saline control group that received n-6 control diet and 2. n-6 received PolyI:C group against n-3 received PolyI:C group. Please see Fig. 2 for global methylation levels in each group and CpG distance to the nearest annotated gene.

2. Experimental design, materials and methods

MIA mouse model was generated by administering a sodium salt of polyI:C to pregnant C57BL6N mice on gestation day-9 (GD9) via the tail vein. Breeding and colony maintaining conditions are described in detail elsewhere [1,3]. Home cages were assigned as experimental units on postnatal day (PND) 21. A total of n = 11 pregnant mice were used. Six were exposed to PolyI:C (5 mg/kg, injection via the tail vein) and 5 to saline vehicle, on gestation day 9. After weaning n = 39 offspring exposed to MIA and n = 38 exposed to saline were split to generate n = 12 MIA units (of 2−6 same-sex offspring); and n = 12 control units (of 2−6 same-sex offspring). The same-sex offspring from each litter were housed together in an experimental unit. The animals were maintained under ad libitum food and water, kept in 12:12 h normal light-dark cycle (lights off at 19:00) and temperature and humidity-controlled (21 ± 1 °C, 55 ± 5%) animal vivarium. Animals in the home cage were not disturbed, except for weekly cage cleaning.

3. Early dietary administration of PUFA

Experimental units were randomly allocated to n-3 PUFA enriched diet or n-6 PUFA control diet by splitting both saline control group and polyI:C group into two halves. Please see Fig. 3 for the study design and the total number of animals used. Mice received approximately 2 gm daily dose of n-3 PUFA from calorific value balanced, modified diet which was created by adding appropriate amounts of n-3 and n-6 PUFA to the rodent AIN93 diet. The diet composition and list of nutrients in the control diet and modified diet is reported elsewhere [1,4]. All diets were purchased from Harlan Laboratories, Madison, USA.

4. Hypothalamus tissue collection and DNA extraction

Mice were sacrificed by cervical dislocation at 12-week of age and hypothalamus was quickly collected in 1.5ml tubes using microdissection on a cold platform. The region of interest was selected by referring to the Allen Mouse Brain Atlas [5] (please see Fig. 4) and the tissue was flash frozen in liquid nitrogen and stored at −80 °C freezer. DNA was extracted in EZ1 Advanced XL using Qiagen EZ1 DNA extraction kit as per manufacturer's protocol. All DNA samples underwent quantification using Nanodrop spectrometry and quality control assessment using gel electrophoresis before being used in the RRBS. Please see Fig. 4 panel C.

5. Reduced representation bisulfite sequencing

Genomic DNA was pooled as per experimental units and RRBS method was used for library preparation. In brief, 2.5 μg of genomic DNA was digested overnight with MspI enzyme (New England Biolabs, Ipswich, MA), using 20 units of enzyme per μg of DNA. The fragments with blunt ends are repaired, forward and reverse adapters are ligated. Fragments of size 150−470bp were selected and bisulfite converted using EZ DNA methylation kit (Zymo Research, Irvine, CA). The fragment sizes were confirmed on a 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA) and quantified in a Qubit 2.0 Fluorometer (Life Technologies, Grand Island, NY). A double-stranded DNA library was produced using Illumina TruSeq DNA library preparation system. These libraries were PCR amplified and single end sequenced in a HiSeq 2000 system with 51bp read length. Please see Fig. 1 panel B for sequence quality analysis results using Fastqc for representative samples, (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/).

6. Data processing

Illumina universal adapter sequences were trimmed from raw reads using cutadapt, maintaining a minimum length of 25 bases. Trimmed reads from 24 samples were aligned to mouse reference genome (mm10) using the BSMAP program by activating RRBS function and minimum fragment length 20bp. Final methylation data reported as the fraction of reads that were methylated was generated
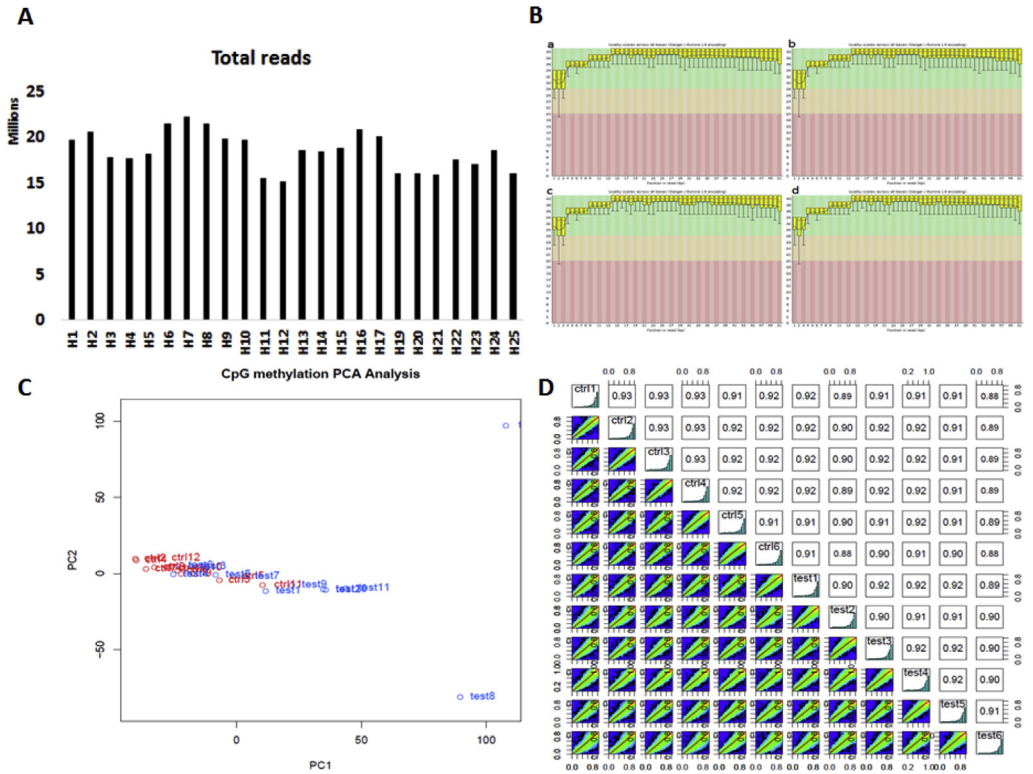
Fig. 1. A. Total number of reads in each sample plotted as millions reads on the y-axis for the corresponding samples on the x-axis. B. Overall sequence read quality of representative samples from each group. a. n3-Saline, b. n-6 Saline, c. n-3 PolyI:C, d. n-6 PolyI:C diet administered groups. Read quality was plotted as Phred score on the y-axis against base position in the reads on the x-axis. C. Principle Component Analysis of the 24 samples with red spots representing saline control samples and blue spots representing polyI:C exposed samples. D. Correlation between samples plotted as scatter plots for n-6 diet administered samples (ctrl 1–6) n-3 diet administered samples (test 1–6).
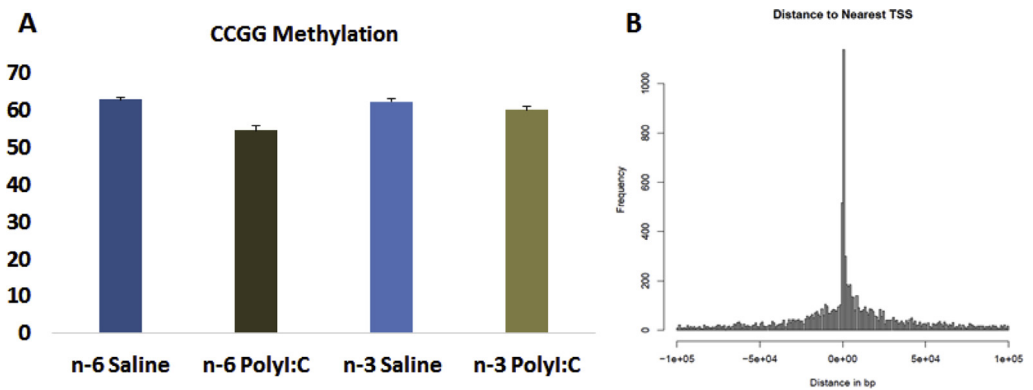

Fig. 2. A. Global methylation in different diet groups plotted as percentage of methylation at CCGG restriction sites. Percentage of methylation is plotted on the y-axis and treatment groups on x-axis. B. Histogram of distance from the CpGs assayed to the nearest TSS was plotted with distance in bp on the x-axis and frequency on the y-axis.
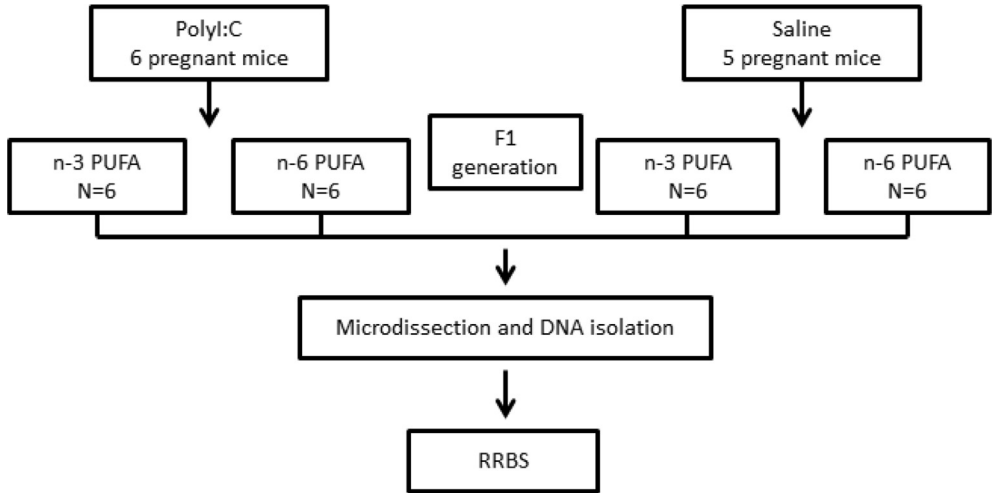
Fig. 3. Study design and number of experimental units used for epigenetic profiling following MIA exposure and dietary intervention.
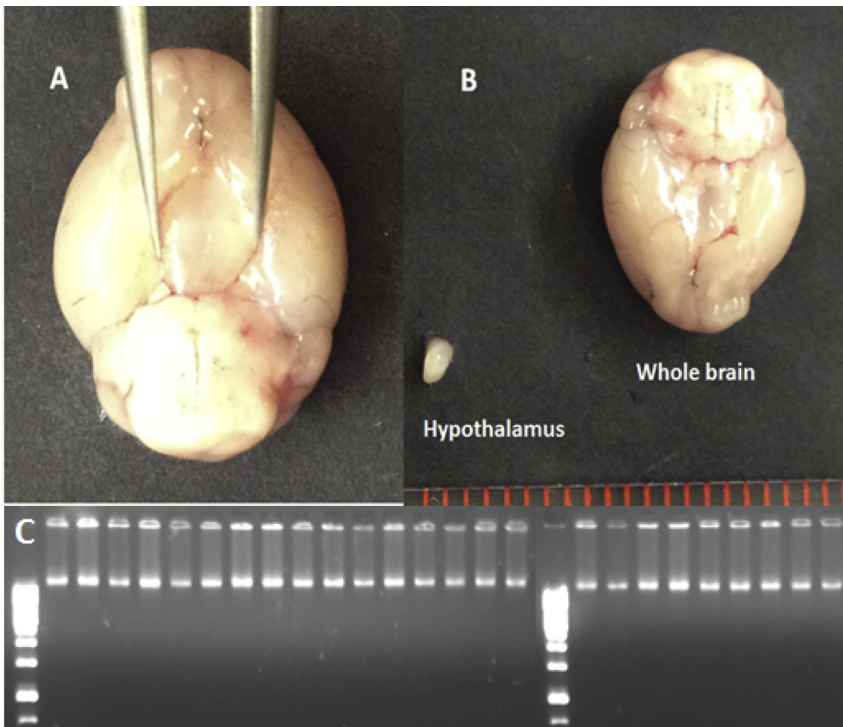

Fig. 4. Hypothalamus was dissected out using microdissection on a cold platform. A. Hypothalamus was selected using a tissue forceps. B. Whole brain and hypothalamus tissue. C. Genomic DNA from hypothalamus samples assayed on 0.7% agarose gel against 10kb marker.

using 'methratio.py' function in BSMAP allowing all Cytosine context. **Statistical analysis, annotation and comparison** of ratio of cytosine bases to total reads for each CpG locations were performed using MethylKit. Please see Fig. 2 for average global methylation level at CpG sites and their distance to the nearest Transcription Start Site (TSS).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

References

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