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Data Article

Dataset of RNA-Seq transcriptome of the fetal liver at day 83 of gestation associated with periconceptual maternal nutrition in beef heifers

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ABSTRACT

Herein, we present a dataset based on the RNA-Seq analysis of liver tissue from bovine female fetuses at day 83 of gestation. The findings were reported in the main article, "Periconceptual maternal nutrition affects fetal liver programming of energy- and lipid-related genes" [1]. These data were generated to investigate the effects of periconceptual maternal vitamin and mineral supplementation and rates of body weight gain on the transcript abundance of genes associated with fetal hepatic metabolism and function. To this end, crossbred Angus beef heifers (n = 35) were randomly

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Dataset link: Transcriptomic profiling of liver tissues of 83 days fetuses in response to early maternal nutrient supplementation (Original data)

Keywords:
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assigned to 1 of 4 treatments in a 2 × 2 factorial design. The main effects tested were vitamin and mineral supplementation (VTM or NoVTM – at least 71 days pre-breeding to day 83 of gestation) and rate of weight gain (low (LG – 0.28 kg/d) or moderate (MG – 0.79 kg/d) – from breeding to day 83). The fetal liver was collected on day 83 ± 0.27 of gestation. After total RNA isolation and quality control, strand-specific RNA libraries were prepared and sequenced on the Illumina® NovaSeq 6000 platform to generate paired-end 150-bp reads. After read mapping and counting, differential expression analysis was performed with edgeR. We identified 591 unique differentially expressed genes across all six vitamin-gain contrasts (FDR ≤ 0.1). To our knowledge, this is the first dataset investigating the fetal liver transcriptome in response to periconceptual maternal vitamin and mineral supplementation and/or the rate of weight gain. The data described in this article provides genes and molecular pathways differentially programming liver development and function.

Specifications Table

Subject	Agricultural and Biological Sciences
Specific subject area	Animal Science, Omics: Transcriptomics
Type of data	RNA-Seq raw data (FASTQ format), text files, figures, and table
How the data were acquired	Total RNA isolation: RNeasy Plus Universal Mini Kit (Qiagen®). Library construction: NEBNext® Ultra™ II Directional RNA Library Prep Kit for Illumina (New England BioLabs®). Sequencing: Paired-end (150 bases × 2) High-throughput sequencing on the Illumina® NovaSeq 6000 platform.
Data format	Raw RNA-Seq files (FASTQ format) Raw read count files (.txt format)
Description of data collection	Fetal liver samples were collected on day 83 of gestation from 31 samples among four treatments [1]. Total RNA was extracted using the RNeasy Plus Universal Mini Kit (Qiagen®). Strand-specific, paired-end RNA libraries were prepared and sequenced at 150 bp reads. Raw fastq files were analyzed, and cleaned reads were mapped to the *B. taurus* reference genome. Read counts from STAR were used for differential gene expression analysis using edgeR.
Data source location	Animal Nutrition and Physiology Center (ANPC) – North Dakota State University. Fargo, North Dakota, USA
Data accessibility	All relevant data (raw and processed RNA-Seq data) [2] were deposited on: Repository name: Gene Expression Omnibus (GEO) **Data identification number**: GSE224419 **Direct URL to data:** https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE224419
Related research article	W.J.S. Diniz, A. K. Ward, K. L. Mccarthy, C. J. Kassetas, F. Baumgaertner, L. P. Reynolds, P. P. Borowicz, K. K. Sedivec, J. D. Kirsch, S. T. Dorsam, T. L. Neville, J. C. Forcherio, R. Scott, J. S. Caton, C. R. Dahlen. (2023). Periconceptual maternal nutrition affects fetal liver programming of energy- and lipid-related genes. ***Animals.*** 13 (2023) 600. https://doi.org/10.3390/ani13040600. [1]

Value of the Data

- This dataset provides insights into the effects of periconceptual maternal nutrition on fetal liver development, programming, and function.
- This dataset can be mined under different bioinformatic approaches to identify novel targets and regulators of fetal liver programming during early gestation.
- Other researchers can use this data for meta-analysis with a transcriptome profile generated at a different time point or maternal diet.
- The dataset could be re-analyzed and integrated with public data to provide a comprehensive expression atlas of the hepatic tissue during early gestation.

Objective

Fetal growth is responsive to maternal nutrient intake. Macro and micronutrients play key roles in several biological functions and are essential for proper fetal development and metabolism. An increased number of studies have shown that maternal nutrition during the second and third trimesters of gestation can lead to long-term effects on offspring metabolism and health – reviewed in [3]. However, major developmental events occur during early gestation, including organogenesis. Additionally, there is still a lack of knowledge regarding the effects of mineral and vitamin supplementation and the rate of body weight gain during early gestation on fetal tissue programming. Therefore, the objective for generating this RNA-Seq dataset was twofold: (1) to identify differentially expressed genes (DEGs) in fetal livers from heifers under different plans of nutrition during early gestation, and (2) to identify biological processes and pathways that underlie hepatic function and metabolism in response to periconceptual maternal nutrition. Further details on the findings based on this dataset were reported in the main article [1]. The dataset herein described is the first one, to the best of our knowledge, that provides a genome-wide expression profile of the fetal liver in response to maternal diet during early gestation.

1. Data Description

We performed a whole transcriptome analysis of liver tissue from 31 female fetuses at day 83 of gestation to investigate the role of maternal vitamin and mineral supplementation and the rate of body weight gain during the periconceptual period on fetal liver transcriptome and the underlying biological pathways. Samples were arranged in a 2×2 factorial design with the main effects of vitamin and mineral supplementation and rate of weight gain [4]. Herein, we describe the strand-specific, RNA-Seq dataset generated on the Illumina® NovaSeq 6000 platform. The raw paired-end reads (fastq files) from 31 samples and the raw gene counts (text file) are publicly available on the GEO database (GEO accession ID: GSE224419). Below are described the files provided within the current data article. Table 1 shows the metadata, including the sample within each treatment, mapping statistics per sample – the number of raw reads, mapped reads, percentage of mapped reads, and the number of replicates per treatment. We generated, on average, 21.45 million cleaned reads per sample (range from 19.7 to 26.7M). On average, 94.5% of the total reads were uniquely mapped.

Fig. 1A shows the read quality (Phred score was > 30) of the sequencing data after fastQC analysis. The RNA-Seq mapping and read counting were performed using the STAR aligner. The mapping statistics results using *–quantMode GeneCounts* and the mapped features from STAR were summarized by MultiQC and are shown in Fig. 1B.

Gene counts were normalized using the *cpm* function from edgeR. The representation of the distributions of RNA-Seq data after normalization (CPM values) for 31 samples within four treatments are shown in Fig. 1C. The boxplot shows a consistent average across the samples in the dataset. The pairwise differential expression analysis between the treatment groups revealed a

Table 1
Descriptive summary of the experimental population and RNA sequencing statistics.

Sample ID	GEO accession number	Reads (Million sequences)				Treatment
		Raw	Clean	Aligned	% Aligned	
LV_15	GSM7021974	21.6	21.4	20.3	94.7%	NoVTM_LG
LV_16	GSM7021975	22.8	22.5	21.2	94.4%	NoVTM_LG
LV_23	GSM7021976	20.8	20.4	19.3	94.7%	NoVTM_LG
LV_25	GSM7021977	22.4	22.2	21.1	95.2%	NoVTM_LG
LV_34	GSM7021978	20.5	20.2	19.1	94.8%	NoVTM_LG
LV_37	GSM7021979	23.5	23.1	21.9	94.7%	NoVTM_LG
LV_52	GSM7021980	23.1	22.7	21.4	94.0%	NoVTM_LG
LV_68	GSM7021981	20.8	20.1	19	94.4%	NoVTM_LG
LV_22	GSM7021982	21.5	21	19.9	94.6%	NoVTM_MG
LV_24	GSM7021983	27.1	26.7	25.2	94.3%	NoVTM_MG
LV_28	GSM7021984	20.7	20.4	19.4	95.0%	NoVTM_MG
LV_3	GSM7021985	23.7	23.4	22.1	94.4%	NoVTM_MG
LV_31	GSM7021986	20	19.7	18.5	94.2%	NoVTM_MG
LV_35	GSM7021987	21.3	20.9	19.7	94.5%	NoVTM_MG
LV_43	GSM7021988	23.3	23	21.8	94.5%	NoVTM_MG
LV_74	GSM7021989	20.4	20.1	18.9	94.2%	NoVTM_MG
LV_18	GSM7021990	20.6	20.3	19.3	95.0%	VTM_LG
LV_29	GSM7021991	20.5	20.2	19.1	94.7%	VTM_LG
LV_36	GSM7021992	20.5	20.2	19.2	94.6%	VTM_LG
LV_41	GSM7021993	20.5	20.2	18.4	91.2%	VTM_LG
LV_46	GSM7021994	22.4	22.1	20.9	94.6%	VTM_LG
LV_59	GSM7021995	23.6	23.3	22	94.5%	VTM_LG
LV_60	GSM7021996	23.2	23	21.6	93.8%	VTM_LG
LV_65	GSM7021997	20.3	20	19	95.2%	VTM_LG
LV_13	GSM7021998	20.9	20.6	19.6	95.0%	VTM_MG
LV_20	GSM7021999	20	19.7	18.7	94.8%	VTM_MG
LV_44	GSM7022000	21.7	21.4	20.3	94.7%	VTM_MG
LV_45	GSM7022001	23.1	22.8	21.6	94.9%	VTM_MG
LV_48	GSM7022002	22.4	22.2	21.2	95.1%	VTM_MG
LV_67	GSM7022003	21.3	21	20	95.4%	VTM_MG
LV_76	GSM7022004	20.5	20.2	19.2	94.7%	VTM_MG
Average		21.77	21.45	20.29	94.5%	VTM_MG

total of 591 differentially expressed genes (DEGs) across all six contrasts (FDR $\leq$ 0.1). The unique and overlapping differentially expressed genes that underlie the main factors of mineral and vitamin and/or rate of weight gain of gain are shown in Fig. 1D. The list of differentially expressed genes is available as a supplementary file within the main manuscript [1].

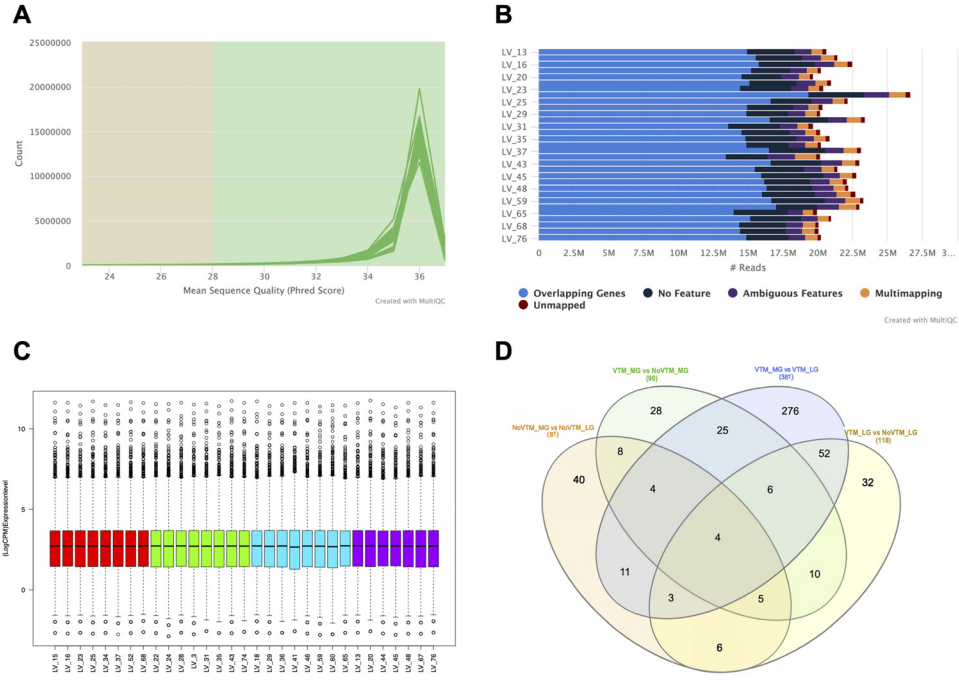

Fig. 1. Overview of the RNA-Seq data and differential expression analyses of the liver of fetuses from heifers receiving or not vitamin-mineral supplementation (VTM or NoVTM) and fed to achieve different rates of body weight gain [low gain (LG) or moderate gain (MG)] during early gestation. (A) Overall Phred score; (B) The statistical results from read mapping; (C) Distributions of RNA-Seq data after normalization (CPM values) for 31 samples within four treatments. The treatments are color coded as red (NoVTM_LG), green (NoVTM_MG), cyan (VTM_LG), and purple (VTM_MG); (D) Number of unique and overlapping differentially expressed genes across contrasts for the main effects of mineral and vitamin and/or rate of weight gain.

2. Experimental Design, Materials and Methods

2.1. Experimental design, treatments, and tissue collection

A 2×2 factorial arrangement of treatments was designed to investigate the main effects of mineral and vitamin supplementation (VTM vs. NoVTM) and rate of body weight gain (low gain [LG] vs. moderate gain [MG]). To this end, crossbred Angus beef heifers were stratified by body weight and randomly assigned to either the VTM or no VTM (NoVTM) supplementation. At breeding, heifers were randomly assigned to either a LG (0.28kg/d) or MG (0.79kg/d). The full description of experimental diets and nutritional composition are described elsewhere [1,3]. Thus, the treatments were arranged as (1) no vitamin and mineral supplementation and low gain (NoVTM_LG, n=9); (2) vitamin and mineral supplementation and low gain (VTM_LG, n=9); (3) no vitamin and mineral supplementation and moderate gain (NoVTM_MG, n=9), and (4) vitamin and mineral supplementation and moderate gain (VTM_MG, n=8).

Heifers were estrus synchronized and bred by artificial insemination using female-sexed semen from a single sire. On day 83±0.27 of gestation, the fetus was removed through ovariohysterectomy and dissected to collect the fetal liver. The liver tissue was snap-frozen on dry ice and stored at − 80 °C.

2.2. RNA isolation, library construction, sequencing, and data processing

To isolate the total RNA from the fetal liver, we used the RNeasy Plus Universal Mini Kit (Qiagen®, Germantown, MA, USA, Cat. #73,404). The RNA quality and purity were evaluated using the Agilent 2100 Bioanalyzer and agarose gel electrophoresis. The RNA quantity was measured using the Qubit™ Broad Range RNA assay kit (ThermoFisher Scientific, Cat. #Q10210). Based on that, 31 samples (n=8 per group, except VTM_MG – n=7) met the quantity and quality parameters for library preparation.

Strand-specific RNA libraries were prepared using the NEBNext® Ultra™ II Directional RNA Library Prep Kit for Illumina (New England BioLabs®, Ipswich, MA, USA). Sequencing was performed on the Illumina® NovaSeq 6000 platform with read lengths of 2× 150 base pairs and an estimated depth of 20 M reads/sample. Library preparation and sequencing were carried out at Novogene Co. (Nanjing, China).

Raw data were cleaned for filtering out sequencing adaptors and reads with a Phred score lower than 30. We used the FastQC v0.11.8 [5] tool for quality control and to estimate read statistics. To aggregate the files from FastQC, we used MultiQC v1.9 [6].

The reads that passed quality control were mapped to the *Bos taurus* reference genome (ARS-UCD 1.2) [7] using the STAR aligner v. 2.7.3a [8] and the gene annotation file (release 100) from the *Ensembl* database. To count the number of mapped reads per gene, the parameter *–quantMode GeneCounts* from STAR was used. The mapping statistic results from STAR were aggregated using the MultiQC software. Next, the read counting files from each sample were concatenated (*read strand aligned with RNA - reverse*) into one dataset and used for differential expression analysis.

2.3. Differential gene expression and functional over-representation analysis

The NOISeq v.2.26.0 [9] and edgeR v.3.24.3 [10] in the RStudio [11] v.1.1.442 environment for R v.3.5.1 [12] were used for post-mapping quality control. The edgeR R-package was used for filtering out genes not expressed or lowly expressed (*filterByExpr* function). Next, the differential expression analysis was carried out using edgeR. All pairwise comparisons between the groups resulted in six contrasts named as follows: (1) VTM_MG vs. NoVTM_LG, (2) VTM_MG vs. VTM_LG, (3) VTM_MG vs. NoVTM_MG, (4) VTM_LG vs. NoVTM_LG, (5) VTM_LG vs. NoVTM_MG, (6) NoVTM_MG vs. NoVTM_LG. Differentially expressed genes (DEGs) were identified after multiple testing corrections of the *p-values* based on the Benjamini-Hochberg methodology (FDR $\leq$ 0.1).

We used the UpSetR v.1.4.0 package [13] to visualize the intersections among different lists (n=6) of differentially expressed genes (DEGs). Furthermore, overlaps across the DEGs list for the main effects of VTM and rate of body weight gain were retrieved using the *InteractiVenn* web tool [14] and represented as Venn diagrams. Biological processes and pathways underlying the DEGs for each contrast were retrieved using the ShinyGo v.0.76.2 web tool [15]. Significant results were identified after *p-value* multiple testing correction (FDR $\leq$ 0.05).

Ethics Statements

All animal experiments followed the relevant guidelines and regulations. The experimental design, animal management, and tissue collection were approved by the North Dakota State University Institutional Animal Care and Use Committee (IACUC #A19012).

Declaration of Competing Interest

Authors J. C. Forcherio and R. Scott are employees of Purina Animal Nutrition LLC (Land O'Lakes, Inc., Arden Hills, MN, USA), which sponsored the sample analysis for this experiment. Purina Animal Nutrition LLC manufactured the Purina® Wind & Rain® Storm® AllSeason 7.5 Complete mineral, the VTM and NoVTM pellets, and the protein/energy supplement used in this study. The funders had no role in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results that were done entirely independently by North Dakota State University and Auburn University personnel.

All the other 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.

Data Availability

Transcriptomic profiling of liver tissues of 83 days fetuses in response to early maternal nutrient supplementation (Original data) (Gene expression omnibus).

CRediT Author Statement

Wellison J.S. Diniz: Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing; **Alison K. Ward:** Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing; **Kacie L. McCarthy:** Conceptualization, Funding acquisition, Investigation; **Cierrah J. Kassetas:** Investigation, Writing – review & editing; **Friederike Baumgaertner:** Investigation, Writing – review & editing; **Lawrence P. Reynolds:** Investigation, Methodology, Writing – review & editing; **Pawel P. Borowicz:** Investigation, Methodology, Writing – review & editing; **Kevin K. Sedivec:** Investigation, Methodology, Writing – review & editing; **James D. Kirsch:** Investigation, Methodology, Writing – review & editing; **Sheri T. Dorsam:** Investigation, Methodology, Writing – review & editing; **Tammi L. Neville:** Investigation, Methodology, Writing – review & editing; **J. Chris Forcherio:** Conceptualization, Methodology, Writing – review & editing; **Ronald Scott:** Conceptualization, Methodology, Writing – review & editing; **Joel S. Caton:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing; **Carl R. Dahlen:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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