Genome-wide Epigenetic Signatures of Family Environment in 9 Year Old Children

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Research on nonhuman animals finds that early life adversity produces important epigenetic changes in that affect later life success. For humans, the limited evidence suggests that the differences the early life environment may also result important epigenetic differences later in life. In this paper we explore the association of early life social and family environments and age 9 methylation patterns using data from the Fragile Families and Child Wellbeing Study (FFS). The FFS is based on a stratified, multistage, probability sample of children born in large US cities between February 1998 and September 2000, with an oversample of children born to unmarried parents (three quarters unwed, one quarter wed; n=4,898). Baseline interviews with mothers and fathers were conducted soon after the child's birth, and subsequent interviews were conducted when the focal child was 1, 3, 5, and 9 years old. Saliva DNA samples were taken at the age-9 followup, by using the Oragene DNA sample collection kit (DNA Genotek). To study how harsh environments might influence the methylation of DNA derived from all three germlines, we identified 40 children and of their mothers based on a two-step process. In the first step the sample was constrained to children meeting the following conditions: 1) they provided saliva at the year 9 (wave 5) in-home interview, 2) self-identified race as black or African-American, and 3) are male, resulting in a subsample of 645 participants. We arrayed the subsample on an index of disadvantage from birth to age 5 based on an equally weighted combination of: 1) a poverty and material hardship measure, 2) an assault and harsh parenting measure, and 3) a parental partner relationship instability measure. Thus, the children who scored lowest on this score typically lived in affluent, nurturing, and stable (and two-parent) families. The children who scored highest on this scale live in high poverty, abusive, and highly unstable families. We selected the 20 lowest and 20 highest scoring boys and also selected 5 paired mothers from each group. Due to insufficient genetic material some results were untenable

leaving us with 17 low-risk boys, 18 high-risk boys, 4 low-risk paired mothers, and 5 high-risk mothers.

The genome-wide methylation pattern was characterized using a MeDIP protocol (immunoprecipitation) with the Nimbelgen 3x720K CpG Island Plus RefSeq Promoter Arrays. This array represents annotated CpG islands as well as the promoters of RefSeq genes derived from the UCSC RefFlat (build NCBI 36, hg18). Raw data was pre-processed using the manufacturer's software, and then subject to quantile normalization followed by processing with ComBat to adjust batch effects[1]. Technical results were excellent, and for selected individual promoters, methylation patterns were consistent with previous reports and X-chromosome inactivation in females. Unsupervised cluster analysis of a subset of high variance probes across 35 children,18 of whom which were from harsh environments (of 600,000 probes that mapped to either RefSeq promoters or CpG islands) indicated that methylation patterns of children from harsh environments were more highly correlated than they were with methylation patterns from children in a less harsh environment. A wide variety of genes were associated with this grouping, including those annotated as transcription factors and immune function genes. Analysis of this dataset is continuing, with the aim of understanding how harsh environments affect promoter methylation of genes within particular functional networks. This establishes that valid biological signatures can be derived from DNA collected from saliva.

[1]Johnson, WE, Rabinovic, A, and Li, C (2007). Adjusting batch effects in microarray expression data using Empirical Bayes methods. Biostatistics 8(1):118-127