Parental Social Disparities in Epigenetic Regulation of Newborns' Imprinted Genes Related to Gestational Growth and Later-Life Health

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Abstract

Children whose parents have lower income and education are at risk for obesity and later-life health risks. Explanations of enduring associations of early-life socioeconomic status (SES) with adult health have focused on stress and behavioral factors, but the biological mechanisms linking these are poorly understood. DNA methylation is the most studied epigenetic mechanism in epidemiologic studies, but social differences in methylation of particular genes are understudied, particularly at birth. We focus on a cluster of particularly well-studied genes, in which methylation is linked to gestational growth, increases childhood obesity risk, and predicts multiple health problems in adulthood. We measured methylation at differentially methylated regions (DMRs) regulating genomically-imprinted genes (*IGF2*, *H19*, *DLK1*, *MEG3*, *PEG1/MEST*, *PEG3*, *PEG10/SGCE*, *NNAT*, and *PLAGL1*) using umbilical cord blood from 619 infants in Durham, North Carolina in 2010-2011. We examined disparities in DMR methylation levels by race/ethnicity of both parents, and the role that maternal SES may play in explaining race/ethnic epigenetic differences. Unadjusted race/ethnic differences were evident only at the *IGF2*, *H19*, *MEG3*, and *NNAT* DMRs (e.g. a 0.83SD (p<0.001) difference in *IGF2* methylation between Black and White fathers). An inverse pattern appeared by race/ethnicity of mothers vs. fathers for *NNAT*. With SES adjustment, race/ethnic differences persisted for the *IGF2* and *NNAT* DMRs. Results suggest social factors may not only influence DNA methylation, but do so in ways that vary by DMR. These findings support the hypothesis that epigenetics is one path through which prenatal social conditions may influence health and health disparities across the lifecourse.

Understanding and reducing health disparities is a key public health goal (Braveman et al., 2011). Segregation, discrimination, and historical processes result in typically worse social and environmental exposures for minorities and the disadvantaged (Diez Roux & Mair, 2010; Link & Phelan, 1995). Differential exposures assorted by race/ethnicity are likely responsible for most health disparities (Hertzman & Boyce, 2010), while the possible role of ancestry-linked genomic factors is not yet fully understood. Emerging evidence blurs the line between "nature and nurture": social and physical risks and resources assorted by race/ethnicity and socioeconomic status (SES) may change how genes are expressed (Champagne, 2010; Szyf et al., 2008). Since the 2008 finding that exposure to famine *in utero* predicts DNA methylation and chronic disease in later life and of offspring (Heijmans et al., 2008; Painter et al., 2008), epigenetic marks which regulate gene expression have been linked to such diverse outcomes as cancer, asthma, and hormonal and metabolic profiles (Pearce et al., 2012; Salam et al., 2012; Uddin et al., 2011; Veenema, 2012; Walters et al., 2013). Thus, epigenetics offers immense hope of explaining causal mechanisms of disease and how disparities are produced. And because many epigenetic factors are malleable, at least within specific time windows, this understanding offers prospects for prevention. Meanwhile, little is known about the nature and mechanisms of social patterning of epigenetic markers (Heijmans & Mill, 2012) over the lifecourse (Madrigano et al., 2012), especially prior to birth. In particular, it has not been established whether social factors differentially influence distinct epigenetic marks.

Recent research has documented that social and physical exposures other than famine may modify DNA methylation, particularly nutrition, psychosocial stressors, and toxicants (Thayer & Kuzawa, 2011), all of which can be socially patterned. Social differences have also

been found in methylation in adult leukocytes from peripheral blood. In two genome-wide methylation studies, one found that early-life SES was associated with methylation differences for a broader range of genes compared to adult SES (2011) and another found that early-life but not adult SES was significant (Lam et al., 2012). In studies of repetitive element DNA methylation (Alu and LINE1), lower methylation was found among respondents with lower SES (McGuinness et al., 2012; Tehranifar et al., 2013) and in Blacks compared to Whites (Zhang et al., 2011), although early life low SES was associated with higher methylation (Tehranifar et al., 2013). In a large diverse population sample, Subramanyam and colleagues (2013) found differences in repetitive element DNA methylation by wealth and by race/ethnicity (which persisted with SES adjustment), but in different directions for the repetitive element DNA measures studied. DNA methylation levels have been shown to persist within an individual from birth to at least age three (Herbstman et al., 2013), and low birth weight has been linked with DNA methylation 20 years later (Wehkalampi et al., 2013). These studies evaluated repetitive elements methylation or genome-wide methylation and thus do not point to loci that improve our understanding of mechanisms specific to particular diseases. However, these findings support the hypothesis that in addition to childhood SES, periconceptional and prenatal socioeconomic status may structure exposure to conditions which influence epigenetic markers in early life, and in turn, that early-life epigenetic disparities influence adult health and disparities.

Even though the epigenome does accumulate changes during the aging process, neonatal exposures that alter establishment of maintenance of these marks may be much more influential (Edwards et al., 2007; Murphy & Jirtle, 2003; Woodfine et al., 2011). Epigenetic marks are "wiped" and replaced during gametogenesis and again early in embryonic development. For most autosomal genes, there is equal probability of expression of both the maternal or paternal

alleles. However, in "imprinted" genes one allele is silenced while the other is expressed in a manner that is dependent on the gender of the parent from whom the particular allele was inherited. This pattern of expression is established by the differential epigenetic marking (including DNA methylation) of the two parental alleles in the gametes, and these marks are faithfully retained throughout prenatal development and maintained in somatic tissues throughout life.

Imprinted genes are critical to appropriate prenatal growth and development. Imprinting defects are associated with a variety of developmental abnormalities and syndromes, including Prader-Willi and Angelman syndromes (Rabinovitz et al., 2012; Rodriguez-Jato et al., 2013), Beckwith-Wiedemann Syndrome (Court et al., 2013), and have been implicated in neurodevelopmental disorders including autism (Badcock & Crespi, 2006; Grafodatskaya et al., 2010). Furthermore, given the importance of these genes to directing appropriate prenatal growth, methylation profiles of the regulatory regions and expression levels of imprinted genes are often found to be highly deregulated in many types of cancer.

This study examined nine differentially methylated regions (DMRs) that are involved in regulating the imprinted expression of paternally expressed *IGF2, DLK1, NNAT, PEG1/MEST, PEG3, PEG10, SGCE, PLAGL1* and maternally expressed *H19* and *MEG3*. The DMRs examined included the paternally methylated *IGF2* DMR, *H19* DMR, *MEG3* DMR and *MEG3-IG* DMR, and the maternally methylated *PEG1/MEST* DMR, *PEG3* DMR, *PEG10/SGCE* DMR, and *PLAGL1* DMR. These imprinted genes (Varrault et al., 2006) were selected for study because they are all known to have important functions in development, some in social behaviors and nurturing (*PEG1/MEST*, *PEG3*) (Ubeda & Gardner, 2011), in maintenance of energy homeostasis and obesity (*IGF2*, *NNAT*, *PLAGL1*, *DLK1*) (Croteau et al., 2005; Heijmans et al.,

2008; Perkins et al., 2012; Sferruzzi-Perri et al., 2013; Vrang et al., 2010), in neurological function (*IGF2, PEG3, NNAT*) (Benarroch, 2012; Johnson et al., 2002), and as non-coding RNAs (*H19, MEG3*) (Gabory et al., 2006; Lu et al., 2013; Zhou et al., 2012), and all of them have been implicated in cancer. As such, this group is among the most intensively studied of the imprinted genes in humans, and the regions demarcated by differential methylation that control the imprinting and expression of these genes are relatively well understood.

We used data from the Newborn Epigenetic STudy (NEST), a birth cohort study in Durham, NC, to investigate the association of DNA methylation at the 9 DMRs of these 10 imprinted genes with race/ethnicity and socioeconomic status. We considered race/ethnicity of both parents, which differed for one quarter of the sample. We then added SES measures in regression models to assess the potential contribution of SES to explaining race/ethnic variation in imprinted gene methylation. We performed these analyses separately for each DMR in order to assess how social influences on DNA methylation may vary by DMR.

MATERIALS AND METHODS

Data

The Newborn Epigenetic STudy (NEST) recruited pregnant women (age 18+) from prenatal clinics who intended to deliver at either of the two obstetric facilities serving Durham, North Carolina (Duke and Durham Regional hospitals) in 2009-2011. DNA methylation of samples of umbilical cord blood leukocytes were evaluated for methylation at 9 DMRs of imprinted genes in 619 newborns. Mothers also completed a questionnaire at enrollment (gestational age at visit averaged 12 weeks). Two-thirds (67%) of the 2,548 women approached consented to participate. Non-respondents were more likely to be Asian or Native American. A

further 396 mothers did not participate, mostly because they did not give birth or did not use a participating hospital (Liu et al., 2012). Chromosomal locations (Skaar et al., 2012) and bisulfite pyrosequencing (Nye et al., 2013) of the cord blood DNA is given elsewhere (Murphy et al., 2012b). The study protocol was approved by the Duke University Institutional Review Board.

Variables and Measurement

Maternal and paternal race/ethnicity was categorized as non-Hispanic Black, Hispanic, Other, and non-Hispanic White (reference category), with an additional category for fathers for whom mothers did not report race/ethnicity. Maternal household income was categorized as follows: less than $25,000; $25,000-50,000; $50,000-$100,000, or more than $100,000 (reference category). Maternal education reference was coded as: up to 12 years; 13-15 years, 16 years (reference category), or 17 years or more. Reference categories were chosen to include sufficient proportions of the sample and provide contrast with other categories. Missing data was represented by categorical variables and not shown, except that missing race/ethnicity of father is shown.

Statistical Analysis

We reported frequencies and percentages of sociodemographic variables, along with summary statistics and analysis of variance (ANOVA) statistics on how methylation of each epigenetic marker varies by sociodemographic group. Several of the epigenetic markers had little meaningful social patterning, so only mean levels were reported for these DMRs.

We used regression models to estimate associations of social factors with methylation. We examined mother's and father's race/ethnicity first in separate models, and then jointly.

Next, to assess the potential contribution of socioeconomic differences by race/ethnicity to overall race/ethnic differences, we examined measures of SES (mother's education and household income) without and with adjustment for parental race/ethnicity. These models do not adjust for potential explanatory variables such as maternal obesity or nutritional factors, because the goal is to assess baseline disparities which may proliferate across the lifecourse and these factors may be causally related.

RESULTS

Study participants were diverse in terms of race/ethnicity and SES (Table 1). Mothers' race/ethnicity was 37% non-Hispanic Black, 29% non-Hispanic White, 31% Hispanic, and 4% Other. Mothers did not report race/ethnicity for 8% of fathers, and reported more fathers as Other and fewer as non-Hispanic White than reported for themselves. Mothers reported different race/ethnic groups for themselves and their baby's father in 24% of the sample, which allows sufficient variation to jointly consider race/ethnicity of both parents. The sample also includes a wide range of income and education levels. There were no significant sociodemographic differences in the number of non-missing markers.

Methylation of the *IGF2*, *H19*, and *MEG3* DMRs (except *H19* DMR and maternal race/ethnicity and education) showed significant unadjusted differences in means across race/ethnicity, income, and education (Table 1). Analyses of variance did not reveal race/ethnic differences or socioeconomic differences for the *PEG3*, *PEG10/SGCE*, *PLAGL1*, *PEG1/MEST*, *MEG3-IG*, or *NNAT* DMRs (mean levels given in Table 2).

Table 3 presents a series of regression analyses for methylation of each DMR for which initial race/ethnic differences were found, as well as for the *NNAT* DMR. Models 1 include only

maternal race/ethnicity, while Models 2 include only paternal race/ethnicity and Models 3 consider race/ethnicities of both parents. Models 4 include only SES, while Models 5 include all covariates. This modeling strategy shows how estimates of disparities change under adjustment for additional covariates.

In Table 3, initial patterns of race/ethnic disparities in Models 1 and 2 were not consistent depending on whether maternal or paternal race/ethnicity is considered, and changed when maternal and paternal race/ethnicity are considered together in Models 3. For the *IGF2* DMR, mean methylation was 51.1%. Newborns with Black and Hispanic fathers, and those for whom paternal race/ethnicity was not reported, have lower methylation of the *IGF2* DMR compared to those with White fathers. These strong paternal race/ethnic differences (Black-White -.83 SD, $p<0.001$; Hispanic-White -.45 SD, $p<0.01$) persisted after adjustment for maternal race/ethnicity in Model 3; however the lower methylation in newborns with Black mothers becomes non-significant, while a significantly higher methylation with Hispanic compared to White mothers appears (.33 SD, $p<0.05$) in models with race/ethnicity of both parents included.

Likewise for the *H19* DMR, the magnitude and direction of the association for maternal race/ethnicity changes after adjustment for paternal race/ethnicity, although these differences remain insignificant. Mean *H19* methylation was 49.2%. Those with Hispanic (-.41 SD, $p<0.05$) and Other (-.56 SD, $p<0.01$) fathers have lower methylation of the *H19* DMR compared to those with White fathers, differences which increased slightly after adjustment for maternal race/ethnicity. For the *MEG3* DMR, mean methylation was 72.3%. Newborns with Black and Hispanic mothers and fathers, and Other fathers, had higher *MEG3* methylation than those with White parents. When both parents were considered together, the paternal differences were eliminated while the higher methylation for those with Black (.44 SD, $p<0.05$) and Hispanic (.41

SD, $p<0.05$) mothers remained. The *NNAT* DMR exhibited no race/ethnic differences when parents were examined separately. In Model 3 when race/ethnicities of both parents were considered in one model, methylation was higher for those with Black (.47 SD, $p<0.05$) and Hispanic (.39 SD, $p<0.05$) mothers, and lower for Black (-.52 SD, $p<0.05$), Hispanic (-.44 SD, $p<0.05$), and those with no race/ethnicity not reported, compared to those with White fathers. That is, the differences in *NNAT* were in opposite directions for mothers and fathers. Mean *NNAT* methylation was 55.1%.

Comparing Models 5 with Models 3 and 4 gives a picture of how race/ethnicity and SES may interact. For the *IGF2* DMR, those with mothers with lower household income (less than $25,000 or $25,000-$50,000 compared to more than $100,000), and with 13-15 or 17 or more years of education had less methylation compared to those with 16 years of maternal education. Education, but not income, differences were apparent after adjustment for race/ethnicity. Adjusting for SES reduced the race/ethnic difference by fathers overall, but the gap in methylation for those with Black fathers remained large and significantly negative (-.68 SD, $p<0.001$). Those with fathers for whom race/ethnicity was not reported also had significantly less *IGF2* DMR methylation, while those with Hispanic (vs. non-Hispanic White) mothers had higher methylation (.35 SD, $p<0.05$). For the *H19* and *MEG3* DMRs, SES differences were not statistically significant, but adjusting for SES left the race/ethnic differences insignificant as well. For the *NNAT* DMR, adjusting for SES statistically explained paternal race/ethnicity differences, but did not weaken the significant association of Black and Hispanic mothers with higher methylation.

Multivariate analyses replicating Table 3 for the other 5 DMRs are presented in Table 4. For the *PEG10/SGCE* and *MEG3-IG* DMRs, newborns with fathers whose race/ethnicity was not

reported had lower methylation than those with White fathers. Those with Black fathers had significantly lower *PEG3* DMR methylation in unadjusted models only. For *PEG1/MEST*, those with Other fathers and with fathers for whom race/ethnicity was not reported had significantly lower methylation before SES adjustment.

The analyses examined 9 DMRs for associations with race/ethnicity and SES, and only some yielded significant differences between groups which would be due to chance less than 5% of the time.

DISCUSSION

In this multiethinic cohort, we hypothesized that SES accounted for some of the racial/ethnic differences in adult disease susceptibility by examining stable DNA methylation marks at DMRs regulating genomically imprinted genes. We found unadjusted race/ethnic and socioeconomic differences in methylation of 3 of 9 differentially methylated regions of imprinted genes examined (*IGF2* DMR, *H19* DMR, *MEG3* DMR), race/ethnic differences alone for 1 (*NNAT*), and weak or no differences for others (*PEG3*, *PEG10/SGCE*, *PLAGL1*, *PEG1/MEST*, and *MEG3-IG* DMRs). These differences across genes were not solely differences in strength of association; distinct patterns were observed linking social conditions with methylation for each gene. For the *IGF2* DMR, an SES gradient appeared even after adjusting for race/ethnicity, while the maternal Hispanic-White and paternal Black-White gaps remained with SES controls. For the *H19* and *MEG3* DMRs, adjusting for SES statistically "explained away" the observed race/ethnic differences. For *NNAT*, those with Hispanic and Black mothers had higher methylation, and with Hispanic and Black fathers had lower methylation, compared to for White parents. However, the social factors examined were not major contributors to the overall variance in methylation ($R^2 < 0.10$, except $R^2 = 0.15$ for *IGF2* DMR). As multiple regions were

examined, Bonferroni correction (0.006) is worth considering, in which case the only remaining differences were at the *IGF2* DMR. However, many genomic studies employing Bonferroni corrections also have much larger sample sizes than is common in birth cohort studies and engender more false positives by testing more parameters.

Using the socioeconomic predictors available, we were not able to explain all of the race/ethnic differences in the *IGF2* and *NNAT* DMRs, especially the remarkably lower (β=-.68, $p<.001$) methylation of the *IGF2* DMR for newborns with Black (vs. White) fathers. An explanation which extends the extant literature is that Black fathers' epigenomes may embody an intergenerational legacy of nutritional/metabolic disadvantage, information that may be carried forward through the germline to subsequent generations. Previous findings show that prenatal exposure to famine (Heijmans et al., 2008) is a risk factor for lower *IGF2* DMR methylation, and that adult offspring of fathers (but not mothers) exposed prenatally to famine had higher BMIs (Veenendaal et al., 2013). Paternal obesity is also a risk factor for lower *IGF2* DMR methylation (Soubry et al., 2013), and lower *IGF2* DMR methylation results in lower plasma insulin-like growth factor and lower birth weight (Hoyo et al., 2012) and greater childhood obesity risk (Perkins et al., 2012), risk of colorectal cancer (Cruz-Correa et al., 2004; Cui et al., 2003), and other conditions (Heijmans et al., 2008; Kim et al., 2006; Möller et al., 2007; Painter et al., 2008). Other factors are also implicated in *IGF2* DMR methylation (Murphy et al., 2012a; Soubry et al., 2011). Whatever the origin, this Black-White gap in *IGF2* DMR methylation at birth should be a target for mechanistic studies of how it may be involved in the disturbing Black-White differences in birth weight and other outcomes (Nepomnyaschy, 2009), with particular attention to fathers. Research on race/ethnic and socioeconomic variation in health outcomes generally finds similar patterns of disparities across health outcomes, with many subtle

differences and notable variations. Previous research on DNA methylation which considered social factors has typically focused on just 2-3 epigenetic measures at a time, notably repetitive sequences such as LINE1 and Alu (McGuinness et al., 2012; Subramanyam et al., 2013; Tehranifar et al., 2013; Zhang et al., 2011), but some studies have undertaken more comprehensive study of methylation across the genome (Borghol et al., 2011; Lam et al., 2012). In either case, researchers looked for and found similar patterns of SES for the differential methylation observed, and it appeared that there was an implicit assumption that social factors would act more generally on methylation itself, rather than targeting particular loci. That is, a tacit assumption has been that the same social factors would predict methylation for any region analyzed. However, some studies did find that particular predictors did not associate identically with all epigenetic markers. For instance, Borghol and colleagues (2011) found variation in which epigenetic markers were linked with adult or childhood SES. The results here underscore the potential for social factors to differentially affect methylation of different regulatory regions. If so, this is a truly exciting finding.

Strengths of the study include a sizeable and socially diverse cohort with data collection occurring at a key point in the lifecourse when postnatal exposures would not yet have come into play, and the use of race/ethnic information on both parents. Because respondents were captured at hospitals within one community, the data here reflect the community's population but do not form a representative sample. (Population-representative birth cohort samples are rare.) Where weak or no social patterning was found for DMRs, it is not clear whether there are indeed no differences or whether they would have been apparent in a larger cohort. Also, given that social gradients appeared by analysis of variance even when not seen in multivariate models, a very large population cohort might have found that social patterning was more robust to adjustment in

multivariate models. In addition, household income and education are reported for mothers, but it may be paternal resources that are relevant to the methylation patterns transmitted from the father. The household income measure used was based on a single question and not adjusted for household size, and maternal income may fluctuate around childbirth, so more sensitive SES measures might have shown stronger gradients.

Another key contribution is the ability to differentiate between maternal and paternal race/ethnic differences. Evolutionary "kinship" theory explains imprinting as a battle between paternal and maternal genes in the offspring for accessing maternal resources (e.g., nutrients through the placenta, maternal caregiving postnatally): maternally inherited DNA is thought to maximize mother's reproductive capacity and the fitness of all her offspring by controlling genes that promote growth, while paternally inherited DNA favors maximizing the fitness and growth of his offspring at the expense of those fathered by other males by controlling genes that limit growth (Moore & Haig, 1991). Extending this theory might have predicted that maternal vs. paternal social conditions would act in opposite directions when observed. This opposing pattern of maternal vs. paternal race/ethnicity appeared clearly for the *NNAT* DMR only. The coefficients for race/ethnicity for *IGF2* and *H19* are consistent with this pattern of opposing signs, but only some coefficients achieve statistical significance. Disparities in *MEG3*, however, appear to be similar for both parents, and probably stem from the mothers' access to resources.

It is noteworthy that methylation of the *IGF2* and *H19* DMRs is established during spermatogenesis. Methylation at the *MEG3* DMR is partially established during spermatogenesis with additional methylation accumulating on the paternally-derived allele post-fertilization. The fidelity of methylation establishment at these paternal DMRs may thus be vulnerable to the prevailing holistic paternal environment. Given that socioeconomic measures were collected

from mothers and reflect maternal resources, it is not clear how methylation may be differentially reflecting the role of socioeconomic resources through the maternal vs. paternal epigenome, or in the gestational environment. As in the case of race/ethnicity and the *NNAT* DMR, socioeconomic variation among mothers could be suppressed if maternal and paternal resources are "warring" and are also highly correlated. However, it does appear that social factors act strongly on some DMRs and weakly or not at all on others.

Social researchers have cast doubt on the utility of genetics in understanding "racial" disparities, given the low rate of genetic differences between race groups, and the mutability of these socially-determined identity categories. Rather, these researchers recommend focus on social and environmental exposures which vary across groups [44]. However, identification of genetic polymorphisms causally linked to important outcomes differing by race is considered useful [45]. The same framework applies to epigenetic social inquiry, but with additional interest because social and contextual modification of inherited epigenetic marks blurs the gene-environment distinction yet may have more profound long-term consequences on human health. Meanwhile, epigenetic markings are unlikely to be retained from very distant ancestors, so racial differences should be interpreted as resulting from social and environmental conditions in recent generations.

Study of social differences in DNA methylation offers promise at unlocking the intergenerational transmission of disadvantage, and to further this aim research in this area should rationally evaluate all potential regions of differential methylation rather than examine repetitive element methylation measures, as some have done. Findings from genome-wide and candidate DMR studies can each contribute crucial insights. For instance, genome-wide analyses can offer a broad view of, for instance, the proportion of genes for which there is a statistical

association between a given predictor (say, early-life SES) and methylation. However, focusing on a few genes in a cluster can help achieve two very important aims: (1) to elucidate the interrelationships among predictors more clearly, and (2) to enable comparisons between DMRs in the differential roles that predictors may play. Crucially, birth cohort studies using umbilical cord blood DNA provide a unique opportunity to examine intergenerational influences such as early life social disadvantage, and the accumulation of disadvantage captured in epigenetic information transmitted from prior generations, before the individual experiences the postnatal environment. Newborns' epigenetic profiles appear to not be "a blank slate," but rather prenatal social factors likely play complex roles in generating epigenetic differences – which persist across the lifecourse and influence future health.

Table 1. Summary Statistics of Participants and Associations with Epigenetic Markers

	N[1]	%	*IGF2*			*H19*			*MEG3*			*NNAT*		
			Mean	SE	*p*	Mean	SE	*p*	Mean	SE	*p*	Mean	SE	*p*
Mother's R/E (Ref=NH White)	177	28.6	52.1	0.4	***	47.2	0.2		70.65	0.5	***	55.1	0.5	
NH Black	227	36.7	49.5	0.3		48.6	0.9		73.07	0.4		55.4	0.5	
Hispanic	193	31.2	52.0	0.4		47.9	0.3		73.18	0.4		55.2	1.4	
Other	22	3.6	50.7	0.7		47.9	0.3		70.95	1.2		54.7	0.5	
Father's R/E (Ref=NH White)	155	25.0	49.4	0.3	***	48.4	0.3	*	72.9	0.4	**	54.8	0.5	
NH Black	218	35.2	52.1	0.4		47.9	0.4		73.0	0.5		54.9	0.5	
Hispanic	138	22.3	52.2	0.6		47.1	0.3		72.7	0.8		56.6	1.2	
Other	58	9.4	52.9	0.5		46.7	0.4		70.8	0.5		55.5	0.4	
Not Reported	50	8.1	48.5	0.8		47.3	0.7		71.8	1.0		53.5	1.0	
Household Income (Ref=>$100K)	145	23.4	53.4	0.9	*	47.6	0.3	+	70.9	0.7	*	54.6	0.8	
<$25K	245	39.6	51.1	0.3		47.9	0.6		71.9	0.3		55.2	0.4	
$25-50K	92	14.9	50.7	0.6		48.2	0.4		70.7	0.8		55.1	1.0	
$50-100K	62	10.0	52.4	0.5		49.1	0.5		71.6	0.6		56.4	0.7	
Not Reported	151	24.4	49.7	0.4		46.7	0.4		73.1	0.5		54.3	0.5	
Education (Ref=1-12 Years)	313	50.6	51.0	0.2	***	47.2	0.2	**	73.3	0.3	**	54.9	0.4	
13-15 Years	97	15.7	50.1	0.5		48.1	0.5		72.2	0.7		55.0	0.7	
16 Years	79	12.8	53.4	0.9		48.8	0.4		71.5	0.7		56.0	0.8	
17+ Years	99	16.0	52.0	0.5		48.3	0.4		70.7	0.6		55.5	0.6	
Not Reported	31	5.0	47.3	1.3		45.6	1.1		70.2	1.3		53.0	1.3	

[1] N for any valid epigenetic marker.

Analyses of variance omit missing data. Note that race/ethnic disparities at the *NNAT* DMR became apparent when race/ethnicities of both parents were jointly considered in Table 3.

*** $p<0.001$; ** $p<0.01$; * $p<0.05$; + $p<0.1$; Consider Bonferroni correction (0.05/9=0.006).

Newborn Epigenetic Study, 2010-2011

Table 2. Summary Statistics for Non-Socially Patterned DMRs

	Mean	Standard Deviation	Minimum	Maximum
MEG3-IG	49.3	3.6	31.2	61.6
PEG3/MEST	43.3	4.8	17.7	78.5
PEG3	36.0	3.2	26.9	70.0
PEG10/SGCE	44.7	6.1	2.2	93.4
PLAGL1	57.1	6.8	0.8	82.6

Newborn Epigenetic Study, 2010-2011

Table 3. Race/ethnic and Socioeconomic Patterning in Methylation at DMRs of Imprinted Genes Which Show Disparities, Standardized Coefficients

	IGF2					*H19*					*MEG3*					*NNAT*				
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5
	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b
Mother's R/E (Ref=NH White)																				
NH Black	-0.50 ***		0.16		0.22	-0.02		0.17		0.21	0.44 ***		0.44 *		0.40 +	0.06		0.47 *		0.49 *
Hispanic	-0.01		0.33 *		0.35 *	-0.19 +		0.13		0.19	0.46 ***		0.41 *		0.31 +	0.11		0.39 *		0.43 *
Other	-0.26		0.03		0.03	0.16		0.42		0.38	0.06		0.01		0.03	0.08		0.23		0.21
Father's R/E (Ref=NH White)																				
NH Black		-0.71 ***	-0.83 ***		-0.68 ***		-0.13	-0.27		-0.08		0.38 ***	0.00		-0.06		-0.12	-0.52 *		-0.48 +
Hispanic		-0.17	-0.45 **		-0.22		-0.32 *	-0.41 *		-0.13		0.40 **	0.06		-0.02		-0.10	-0.44 *		-0.34
Other		-0.14	-0.30 +		-0.14		-0.44 **	-0.56 **		-0.37 +		0.34 *	0.12		0.07		0.19	-0.08		-0.02
Not Reported		-0.87 ***	-1.03 ***		-0.55 *		-0.29	-0.37		0.05		0.18	-0.03		0.17		-0.35 +	-0.58 **		-0.41
Education (Ref=16Years)																				
1-12 Years				-0.29 +	-0.31 +				-0.28	-0.29				0.19	0.10				-0.20	-0.22
13-15 Years				-0.51 **	-0.41 *				-0.10	-0.12				0.07	-0.01				-0.19	-0.20
17+ Years				-0.34 *	-0.34 *				-0.15	-0.15				-0.14	-0.13				-0.05	-0.05
Household Income (Ref=>$100K)																				
<$25K				-0.39 *	-0.24				-0.24	-0.27				0.17	0.03				0.23	0.24
$25-50K				-0.50 **	-0.37 +				-0.26	-0.28				-0.15	-0.27				0.16	0.16
$50-100K				-0.22	-0.18				-0.23	-0.24				0.09	0.03				0.32 +	0.31
Constant	0.18 *	0.36 ***	0.33 ***	0.70 ***	0.72 ***	0.06	0.18 *	0.15 +	0.46 **	0.43 *	-0.31 ***	-0.27 **	-0.32 ***	-0.18	-0.24	-0.06	0.07	0.03	-0.03	-0.06
R^2	0.05	0.11	0.12	0.08	0.15	0.01	0.02	0.03	0.04	0.05	0.04	0.03	0.04	0.05	0.07	0.00	0.01	0.03	0.02	0.04
N	556	556	556	556	556	501	501	501	501	501	518	518	518	518	518	458	458	458	458	458
AIC (Lower: Better Model Fit)	1554.4	1523.2	1524.4	1546.4	1519.7	1424.6	1420.1	1423.6	1418.5	1425.6	1454.5	1464.5	1461.9	1461.2	1466.3	1305.9	1302.2	1301.8	1308.6	1311.2

*** p<0.001; ** p<0.01; * p<0.05; + p<0.1

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The models progressively add predictors to examine how joint consideration of maternal and paternal race/ethnicity (Models 3) and race/ethnicity and SES (Models 5) reveal complex social disparities in DNA methylation, patterns which vary by DMR.

Table 4. Race/ethnic and Socioeconomic Patterning in Methylation at DMRs of Imprinted Genes Which Show Few Disparities, Standardized Coefficients

	DLK1					*PEG3*					*PLAGL1*					*PEG10/SGCE*					*PEG3/MEST*				
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5	Model 1	Model 2	Model 3	Model 4	Model 5
	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b
Mother's R/E (Ref=NH White)																									
NH Black	-0.29		-0.06		0.14	-0.46		0.43		0.45	-0.37		1.04		1.25	-0.22		1.32		1.83	-0.41		0.50		0.58
Hispanic	0.41		0.41		0.47	-0.15		0.00		-0.11	-0.84		-0.88		-0.62	-1.20 +		-0.12		-0.13	-0.51		-0.18		-0.21
Other	-0.13		-0.33		-0.32	-0.73		-0.22		-0.28	0.34		0.71		0.64	0.71		1.89		1.93	-0.96		-0.03		-0.36
Father's R/E (Ref=NH White)																									
NH Black		-0.40	-0.34		-0.24		-0.75 *	-1.13 +		-1.13		-0.78	-1.73		-1.82		-0.91	-2.08 +		-1.34		-0.81	-1.26		-0.92
Hispanic		0.50	0.14		0.54		-0.11	-0.12		-0.04		-0.63	0.17		0.17		-1.38 +	-1.20		0.22		-0.43	-0.28		0.16
Other		0.62	0.51		0.66		-0.70	-0.72		-0.71		0.29	0.38		0.25		-1.04	-1.42		-0.41		-1.78 *	-1.78 +		-1.46
Not Reported		-3.32 ***	-3.49 ***		-1.33		-0.83	-0.88		-0.15		-2.28 +	-2.07		-2.54		-4.55 ***	-4.79 ***		-0.57		-2.31 **	-2.32 *		-1.31
Education (Ref=16Years)																									
1-12 Years				-0.28	-0.54				-0.84	-0.82				-1.25	-1.09				-1.71 +	-1.63				-0.90	-0.86
13-15 Years				-0.39	-0.44				-0.83	-0.77				-1.74	-1.73				-1.78 +	-1.88 +				-0.91	-0.99
17+ Years				-0.13	-0.20				-0.23	-0.21				-0.40	-0.47				-1.33	-1.34				0.51	0.51
Household Income (Ref=>$100K)																									
<$25K				1.22 +	1.08				-0.01	0.31				1.05	1.31				-0.90	-1.06				0.70	0.97
$25-50K				1.02	0.99				-0.13	0.13				1.48	1.68				-0.46	-0.56				0.71	1.00
$50-100K				1.71 **	1.72 **				-0.71	-0.62				0.94	0.95				0.16	0.13				1.23	1.34
Constant	49.21 ***	49.39 ***	49.38 ***	48.64 ***	48.64 ***	36.29 ***	36.47 ***	36.46 ***	36.82 ***	36.95 ***	57.53 ***	57.72 ***	57.70 ***	57.38 ***	57.49 ***	45.12 ***	45.80 ***	45.71 ***	46.99 ***	46.88 ***	43.63 ***	44.01 ***	44.01 ***	43.04 ***	43.17 **
R^2	0.01	0.06	0.07	0.09	0.11	0.01	0.01	0.01	0.02	0.03	0.00	0.01	0.01	0.01	0.02	0.01	0.04	0.04	0.07	0.08	0.00	0.02	0.02	0.03	0.04
N	463	463	463	463	463	526	526	526	526	526	573	573	573	573	573	530	530	530	530	530	503	503	503	503	503
AIC (Lower: Better Model Fit)	2495	2469	2474	2464	2468	2714	2712	2717	2719	2727	3826	3824	3828	3831	3840	3412	3398	3401	3388	3398	3001	2995	3000	3000	3009

*** p<0.001; ** p<0.01; * p<0.05; + p<0.1

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