HHS Public Access

Author manuscript

J Epidemiol Community Health. Author manuscript; available in PMC 2015 July 01.

Published in final edited form as:

J Epidemiol Community Health. 2015 July ; 69(7): 639–647. doi:10.1136/jech-2014-204781.

Epigenetic regulation of Newborns' imprinted genes related to gestational growth: patterning by parental race/ethnicity and maternal socioeconomic status

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Abstract

Background—Children born to parents with lower income and education are at risk for obesity and later-life risk of common chronic diseases, and epigenetics has been hypothesised to link these associations. However, epigenetic targets are unknown. We focus on a cluster of well-characterised genomically imprinted genes because their monoallelic expression is regulated by DNA methylation at differentially methylated regions (DMRs), are critical in fetal growth, and DNA methylation patterns at birth have been associated with increased risk of birth weight extremes and overweight status or obesity in early childhood.

Methods—We measured DNA methylation at DMRs regulating genomically imprinted domains (*IGF2/H19*, *DLK1/MEG3*, *NNAT* and *PLAGL1*) using umbilical cord blood leucocytes from 619 infants recruited in Durham, North Carolina in 2010–2011. We examined differences in DNA methylation levels by race/ethnicity of both parents, and the role that maternal socioeconomic status (SES) may play in the association between race/ethnic epigenetic differences.

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Contributors KK designed the study, performed the analysis and wrote the paper. SM and CH edited the paper and collected the data.

Competing interests None.

Ethics approval Duke University Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Per the IRB agreement, data are restricted and only available to study key personnel who are affiliated with Duke University.

Results—Unadjusted race/ethnic differences only were evident for DMRs regulating *MEG3* and *IGF2*; race/ethnic differences persisted in *IGF2/H19* and *NNAT* after accounting for income and education.

Conclusions—Results suggest that parental factors may not only influence DNA methylation, but also do so in ways that vary by DMR. Findings support the hypothesis that epigenetics may link the observed lower SES during the prenatal period and poor outcomes such as low birth weight; lower birth weight has previously been associated with adult-onset chronic diseases and conditions that include cardiovascular diseases, diabetes, obesity and some cancers.

Understanding and reducing health disparities is a key public health goal.[1] Segregation, discrimination and historical processes result in typically worse social and environmental exposures for minorities and the disadvantaged.[23] Emerging evidence blurs the line between 'nature and nurture': social and physical risks and resources by race/ethnicity and socioeconomic status (SES) may change gene expression.[4–9] Meanwhile, genetic ancestry-linked differences also influence DNA methylation (DNA methylation),[10–14] although genetic and environmental origins of population differences still need to be disentangled. In 2008, exposure to famine in utero was found to predict chronic disease in later life and of offspring, and DNA methylation was found to differ between individuals exposed to famine in utero and their same sex siblings at the well-studied IGF2 imprinted domain.[1516] Since then, aberrantly established epigenetic marks which regulate gene expression have been linked to such diverse outcomes as cancer, asthma, birth weight and hormonal and metabolic profiles.[17–22] Thus, epigenetic research may help describe causal mechanisms for how social resources and risks 'get under the skin' and become manifest in health outcomes and disparities therein. Since many epigenetic factors are malleable, at least within specific time windows, this understanding offers prospects for prevention and treatment. Meanwhile, little is known about how social patterns may influence epigenetic marks[23] in early life[24] or gestation. In particular, it is unclear whether social factors differentially relate to distinct epigenetic marks, and whether there may be parent of origin-specific patterns.

Social differences appear in DNA methylation in adult leucocytes. In two genome-wide DNA methylation studies, one found that early-life SES predicted DNA methylation differences for a broader range of genes compared to adult SES[6] and another found differential DNA methylation by early-life SES (but not adult SES).[8] In studies of repetitive element DNA methylation (Alu and LINE1), lower DNA methylation appeared among respondents with lower SES[925] and in blacks,[5] although early-life low SES predicted higher DNA methylation.[25] A large population sample[4] revealed differences in repetitive element DNA methylation by wealth and by race/ethnicity (which persisted with SES adjustment), but in different directions by measure. These studies evaluated repetitive elements or genome-wide DNA 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 SES may structure exposure to conditions which influence epigenetic markers in early life. It is plausible that early-life epigenetic disparities may influence adult health and disparities, but further study is needed.

Once established during early life, DNA methylation patterns in a tissue are not permanent, but appear to persist over time,[24,26,27] including from birth to at least age 3.[7] Low birth weight has been linked with DNA methylation 20 years later.[28] Social and physical exposures such as nutrition, psychosocial stressors and toxicants,[29] all of which can be socially patterned, change DNA methylation. Methylation patterns can change with ageing.[30,31] However, neonatal exposures that alter the establishment or maintenance of these marks may be much more influential than exposures during the life course.[32–34] 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, 'imprinted' gene expression is specific to the sex of the parent, established by the differential epigenetic marking of the two parental alleles in the gametes such that the resulting zygote will have methylation on only one of the two inherited chromosomes at these 'differentially methylated regions' (DMRs). The expected theoretical level of methylation at these DMRs is therefore 50% when cells are analysed, since each has one chromosome with methylation and the same sequence on the other chromosome is unmethylated. These marks are faithfully retained throughout prenatal development and in somatic tissues throughout life. Thus, imprinted gene regulatory regions normally exhibit both temporal and spatial stability[32] compared to non-imprinted regions.

Imprinted genes are critical to appropriate prenatal growth and development. Clearly, severe defects where imprinted status is lost—whether due to genetic defects (eg, loss or gain of the chromosomal region or the entire chromosome) or to epigenetic defects (loss or gain of methylation)—lead to pregnancy failures[35] or to severe developmental and neurological disorders, including the Prader-Willi and Angelman syndromes,[36,37] Beckwith-Wiedemann syndrome[38] and neurodevelopmental disorders such as autism.[39,40] Furthermore, given the importance of these genes in directing appropriate prenatal growth,[22] DNA methylation profiles of the regulatory regions and expression levels of imprinted genes are often found to be highly deregulated in many types of cancer.[41,42] It is presently unclear how small differences in methylation at imprinted DMRs alter the imprinting status or affect the outcome. However, we have previously shown that a 1% change in methylation at the *IGF2* DMR is associated with a twofold change in *IGF2* transcription, and that this was associated with differences in birth weight.[43] Long-term prospective studies are needed to better understand how small magnitude shifts in methylation and/or imprint status contribute to chronic disorders or diseases in adulthood.

This study examined 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 (3 CpG sites), *H19* DMR (4), *MEG3* DMR (8) and *MEG3-IG* DMR (4), and the maternally methylated *PEG1/MEST* DMR (4), *PEG3* DMR (10), *PEG10/SGCE* DMR (6), *NNAT* DMR (3) and *PLAGL1* DMR (6). An estimated 1–5% of genes are imprinted;[44] 65 imprinted genes are documented.[32] We have developed assays for 25 of these regions,[45] over-selecting for growth effectors. Of these we examined nine DMRs[46] because they are all known to have important functions in development, some in social behaviours and nurturing (*PEG1/MEST*, *PEG3*),[47] in maintenance of energy homoeostasis

and obesity (*IGF2*, *NNAT*, *PLAGL1*, *DLK1*),[1548–51] in neurological function (*IGF2*, *PEG3*, *NNAT*),[5253] and as non-coding RNAs (*H19*, *MEG3*),[54–56] and all of them have been implicated in cancer. Thus, this group is among the most intensively studied of the imprinted genes in humans, and the regions demarcated by differential DNA methylation that control 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, North Carolina, to investigate the association of racial/ethnic social identity with DNA methylation at the nine DMRs regulating genomically imprinted genes, which also predict variations in birth weight (a risk factor for common chronic diseases and conditions). We hypothesise that SES (maternal education, household income) may explain some of the associations. Separately by DMR, we considered race/ethnicity of both parents, which differed for a quarter of the sample, separately and then jointly, and assessed the potential contribution of SES to race/ethnic variation in imprinted gene methylation.

MATERIALS AND METHODS

Data

The NEST recruited pregnant women (age 18+) from six prenatal clinics who intended to deliver at either of the two obstetric facilities serving Durham, North Carolina (Duke and Durham Regional hospitals), enabling collection of umbilical cord blood at birth.[5758] Overall the two NEST waves (2006–2008 and 2009–2011), approached 3646 pregnant women ≥18 and 70% (n=2534) were consented, with successful umbilical cord blood collection at delivery for 2214. Enrolment occurred during the first prenatal clinic visit (~13 weeks) with questionnaire and peripheral blood collected. DNA methylation of samples of umbilical cord blood leucocytes was evaluated at nine DMRs of imprinted genes among the first 619 newborns from the second wave.

Although epigenetic marks in some regions may vary by cell and tissue type, we have conducted studies of buccal cells, mono-nuclear and polymorphonuclear cells[5960] and cell type differences in DNA methylation marks in these regions were not detected. Umbilical cord blood contains a number of cell types and it is possible that each cell type exhibits a different pattern of methylation. This is unlikely at imprinted gene DMRs at which methylation is established during early development (during gametogenesis in the prior generation and for some regions, just after fertilisation). Since this occurs prior to gastrulation and tissue differentiation and because DNA methylation is generally somatically heritable, the methylation profiles that are established in early life are faithfully maintained, which we have shown is the case in human fetal tissues[5] and others have shown to be true in adult somatic tissues.[6] Nevertheless, we did analyse fractionated umbilical cord blood, examining the two major components—peripheral blood mono-nuclear cells and polymorphonuclear cells—and found that the level of methylation in these fractions was indistinguishable for all DMRs except MEG3-IG, for which the difference was 1.1% between fractions.[5] Because of these prior published results, we believe it very unlikely that the heterogeneity of cells, at least the major fractions in cord blood, influenced our findings. Cord blood is also accessible and non-invasive compared to other tissue types (eg, foreskins,

organ tissue from autopsies, buccal cells), and is collected before the ex utero environment can influence the epigenome.

Chromosomal locations, bisulfite pyrosequencing conditions, and assay validation are reported elsewhere.[5961] Briefly, genomic DNA (800 ng) was modified with sodium bisulfite, which converts unmethylated cytosines to uracils while leaving methylated cytosines unchanged. Pyrosequencing results in measurement of the percentage of methylated cytosine at each CpG dinucleotide position within the targeted sequence, and assesses non-CpG cytosines within every sample/region analysed for completeness of conversion. Samples were analysed in 96-well plates on a Qiagen PyroMark Q96 MD Pyrosequencer, with no template controls, fully unmethylated and methylated DNA (Epitect Control DNAs, Qiagen; Valencia, California, USA) and a 50:50 mixture of the methylated and unmethylated control. Interplate variability was tested. Within plates, results are averaged for a given DMR. Samples with values ±2 SD from the mean were rerun and averaged. The average SD between original and repeat runs was 1.37% with a range of 0.02–3.9%. On average, one to two samples were rerun per plate. For each DMR methylation was examined at 3–10 CpG sites, and the mean taken. The Duke University Institutional Review Board approved the study protocol.

Variables and measurement

Maternal and paternal race/ethnicity was categorised as non-Hispanic black, Hispanic, Other and non-Hispanic white, with an additional category for fathers for whom mothers did not report race/ethnicity (MRE). Limited SES measures were available. Mothers reported their household income as: less than $25 000, $25 000–$50 000, $50 000–$100 000 or more than $100 000. Maternal education reference was coded as: up to 12; 13–15, 16 or 17 years or more. Categorical variables represent missing income/education data.

Statistical analysis

We reported frequencies and percentages of sociodemographic variables, along with summary and analysis of variance statistics on how DNA methylation of each epigenetic marker varies by sociodemographic group. Several DMRs had little meaningful social patterning, so results for these DMRs are reported separately in table 5. Analyses used Stata statistical software.[62] DNA methylation percentages for the DMRs examined were roughly normally distributed. Standardised coefficients are used to facilitate comparison across DMRs.

We used regression models to estimate associations of social factors with DNA 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) with and without adjustment for parental race/ethnicity. There may be a great many reasons for social differences. We do not adjust for such potential explanatory variables (eg, maternal nutrition, psychosocial stressors or toxic exposures), because the goal is to assess baseline social differences and these factors may be causally related. In

supplementary analyses, we found no problems from multicollinearity (variance inflation factors <5) or outliers (using Cook's influence) in the data.

RESULTS

Study participants were racially/ethnically and socioeconomically diverse (table 1). MRE for 8% of fathers, reported more fathers as Other and fewer as non-Hispanic white than reported for themselves, and gave different race/ethnic groups for themselves and their baby's father in 24% of the sample. Missingness did not differ by sociodemographics.

Table 1 shows that DNA methylation means differed by maternal and paternal race/ethnicity, income and education at the *IGF2*, *H19* and *MEG3* DMRs (except the *H19* DMR did not differ by maternal race/ethnicity and education). 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. Initial patterns in models 1 and 2 were not consistent by maternal versus paternal race/ethnicity, and changed when maternal and paternal race/ethnicity were considered together in model 3. Unstandardised coefficients are given in table 4.

Newborns with black (−0.83 SD, $p<0.001$) and Hispanic (−0.45 SD, $p<0.01$) versus white fathers have lower methylation of the *IGF2* DMR, which persists after SES adjustment. In models with race/ethnicity of both parents included, the lower methylation in newborns with black mothers becomes non-significant, while a significantly higher methylation for Hispanic mothers appears (0.33 SD, $p<0.05$).

For the *H19* DMR, those with Hispanic (−0.41 SD, $p<0.05$) and Other (−0.56 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. Newborns with black and Hispanic mothers and fathers, and Other fathers, had higher *MEG3* methylation. When considering both parents, the paternal differences were eliminated while the higher methylation for those with black (0.44 SD, $p<0.05$) and Hispanic (0.41 SD, $p<0.05$) mothers remained. The *NNAT* DMR exhibited no race/ethnic differences when parents were examined separately, but considered together, methylation was higher for those with black (0.47 SD, $p<0.05$) and Hispanic (0.39 SD, $p<0.05$) mothers, and lower for black (−0.52 SD, $p<0.05$), Hispanic (−0.44 SD, $p<0.05$) and MRE fathers. That is, the differences in *NNAT* were in opposite directions for mothers and fathers.

Incorporating both race/ethnicity and SES together in model 5 and comparing with earlier models which only adjusted for race/ethnicity or SES allows us to see how considering SES affects estimates of disparities. That is, since there are race/ethnic differences in SES, reduced disparities in SES-adjusted models indicate that race/ethnic differences are due to differences in exposures and access to resources. However, since our SES measures are simple, the remaining race/ethnic gaps are not automatically ancestry linked but rather may still have a social component. For the *IGF2* DMR, education but not income, differences

were apparent after adjustment for race/ethnicity. Adjusting for SES reduced the paternal race/ethnic difference, but the gap in methylation for those with black fathers remained large and significantly negative (−0.68 SD, p<0.001). Those with MRE versus white fathers also had significantly less *IGF2* DMR methylation, while those with Hispanic mothers had higher methylation (0.35 SD, p<0.05). For the *H19* and *MEG3* DMRs, SES differences were non-significant, but SES-adjustment 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.

Multivariable analyses replicating table 3 for the other five DMRs are presented in table 5. For the *PEG10/SGCE* and *MEG3-IG* DMRs, newborns with MRE fathers had lower methylation. Those with black fathers had significantly lower *PEG3* DMR methylation in unadjusted models only. For *PEG1/MEST*, those with Other and MRE fathers had significantly lower methylation before SES adjustment.

DISCUSSION

In this multiethnic cohort, we hypothesised that SES accounted for some of the racial/ethnic differences in DNA methylation by examining DMRs regulating genomically imprinted genes. We found unadjusted race/ethnic and socioeconomic (measured by education) differences in DNA methylation of three of nine DMRs of imprinted genes examined (*IGF2*, *H19*, *MEG3*), race/ethnic differences alone for one (*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 DNA methylation for each gene. An SES gradient appeared for the *IGF2* DMR 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 DNA methylation, where those with Hispanic and black fathers had lower DNA methylation, compared to for white parents. However, the social factors examined were not major contributors to the overall variance in DNA methylation (R^2<0.10, except R^2=0.15 for *IGF2* DMR). With Bonferroni correction (p<0.006), the only remaining differences were at the *IGF2* DMR. Observed differences in DNA methylation (<5.3% across social groups) were of a similar magnitude to those reported previously in relation to the Dutch famine (2–5%)[15] or maternal smoking (1–3%).[4363]

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 lower methylation of the *IGF2* DMR for newborns with black fathers. Previous findings show that prenatal exposure to famine[15] predicts lower *IGF2* DMR methylation, and that adult offspring of fathers (but not mothers) exposed prenatally to famine had higher BMIs.[64] Paternal obesity[65] and maternal depression/antidepressant use[66] predict lower *IGF2* DMR methylation, and lower *IGF2* DMR methylation has been linked to lower plasma IGF and lower birth weight[67] and greater childhood obesity risk,[49] presumably due to rapid early growth, risk of colorectal

cancer[4168] and other conditions.[15166970] A speculative 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.[7165] Since reprogramming of imprint methylation marks in males is finalised during sperm maturation, it is also possible that the disadvantage that the father is experiencing in the time span of sperm generation (~64 days in humans), prior to conception, affects a shift in methylation reprogramming that is directly transmitted to the zygote. Methylation quantitative trait loci analysis could be used to search for a genetic origin. Whatever the origin, this paternal 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.[72]

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 (eg, nutrients through the placenta, care-giving postnatally): maternally inherited DNA is thought to maximise the mother's reproductive capacity and the fitness of all her offspring by controlling genes that promote growth, while paternally inherited DNA favours maximising the fitness and growth of his offspring versus those fathered by other males by controlling genes that limit growth.[73] Extending this theory predicts that maternal/paternal social conditions would act in opposite directions, a pattern which appeared clearly in the race/ethnic coefficients for *NNAT* but is consistent with *IGF2* and *H19*. Disparities in *MEG3*, however, appear similar for both parents, and probably stem from maternal resources. Socioeconomic variation among mothers could be suppressed if maternal and paternal resources are 'warring' and mothers and fathers have similar SES. However, it does appear that social factors act strongly on some DMRs and weakly or not at all on others.

Study strengths include a sizeable, socially diverse cohort with data collection occurring at a key point in the life course when postnatal exposures would not yet have come into play, and the use of race/ethnic information on both parents. Since respondents were captured at hospitals within one community, the data here reflect the community's population but do not form a representative sample. Perhaps stronger social patterning would have been apparent in a larger cohort. More sensitive SES measures might have shown stronger gradients. In addition, it may be paternal resources that are relevant under paternal DNA methylation. Future research will explore the potential role of fathers' characteristics in DNA methylation at birth. Given the measures available and sample size, we cannot fully explore the potential for exposures and behaviours which differ by race/ethnicity and SES to contribute to disparities. We use race/ethnic reports by the mother rather than genetic measures, due to our emphasis on social aspects; results using genetic measures may differ. We have examined only nine DMRs, and only in cord blood. We did not examine the relationship between methylation and expression, or how methylation shifts observed may or may not be related to alterations in imprinting status of the genes in the domains analysed. However, the genes we study are known to be involved in growth and perturbed very early in life.

Previous research on DNA methylation which considered social factors has typically focused on either repetitive sequences such as LINE1 and Alu,[45925] or epigenome-wide

DNA methylation studies.[68] Our findings are descriptive, but bring attention to the value of DMR-specific social epidemiological research. 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 including genomic differences 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 and other factors most likely play complex roles in generating epigenetic differences.

Acknowledgments

This work was based on the Newborn Epigenetic Study supported by the National Institute of Environmental Health Sciences of the National Institutes of Health under Award Number R01ES016772. This work was also supported in part by an appointment to the Research Participation Programme for the US Environmental Protection Agency, Office of Research and Development, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the EPA. This work does not represent the official policies of the Environmental Protection Agency.

Funding This work was supported by the DOE/EPA ORISE Fellowship, and also by US Department of Health and Human Services-National Institutes of Health-National Institute of Environmental Health Sciences (R01ES016772).

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What is already known on this subject?

Epigenetic regulation of imprinted genes associates with birth weight. Social disparities have been shown in repeated elements DNA methylation and epigenome-wide in limited studies in adults. It is not known if social disparities in DNA methylation exist at birth and how they may vary by epigenetic marker.

What this study adds?

Race/ethnic differences appeared in methylation at four of nine imprinted gene regions examined in umbilical cord blood, notably a difference between newborns of black versus white fathers at the IGF2 locus, which has been linked to birth weight. Epigenetic social disparities differ by gene and by parent of origin. Differences in DNA methylation patterns may not only influence fetal health but also have the potential to affect adult health disparities.

J Epidemiol Community Health. Author manuscript; available in PMC 2015 July 01.

Table 1

Summary statistics of participants and associations with epigenetic markers

			IGF2			***H19***			***MEG3***			***NNAT***		
	N[†]	**%**	**Mean**	**SE**	**p Value**	**Mean**	**SE**	**p Value**	**Mean**	**SE**	**p Value**	**Mean**	**SE**	**p Value**
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	
Mother's household income (Ref=>$100K)	145	23.4	53.4	0.9	*	47.6	0.3	+	70.9	0.7	*	54.6	0.8	
<$25K	169	27.3	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	
Mother's 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	

Analyses of variance omit missing data. Note that R/E disparities at the NNAT DMR became apparent when R/Es of both parents were jointly considered in table 3.

*p<0.05;

**p<0.01;

***p<0.001;

+p<0.1; Newborn Epigenetic Study, cord blood leucocytes, 2010–2011.

†N for any valid epigenetic marker.

DMR, differentially methylated region; NH, non-Hispanic; R/E, race/ethnicity.

Table 2

Summary statistics for non-socially variant DMRs

DMR	Mean	SD	Minimum	Maximum
MEG3-IG	49.3	3.6	31.2	61.6
MEST1	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/HYMA1	57.1	6.8	0.8	82.6

Newborn Epigenetic Study, cord blood leucocytes, 2010–2011.

DMR, differentially methylated region.

Table 3

Race/ethnic and socioeconomic patterning in DNA methylation at DMRs of imprinted genes which show disparities, standardised 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=16 years)																				
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≥$100 K)																				
<;$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

Newborn Epigenetic Study, cord blood leucocytes, 2010–2011.

The models progressively add predictors to examine how a joint consideration of maternal and paternal race/ethnicity (model 3) and race/ethnicity and SES (model 5) reveals complex social differences in DNA methylation patterns at multiple DMRs.

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

AIC, akaike information criterion; DMR, differentially methylated region; NH, non-Hispanic; R/E, race/ethnicity; SES, socioeconomic status.

Table 4

Race/ethnic and socioeconomic patterning in DNA methylation at DMRs of imprinted genes which show disparities, unstandardised 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	−2.52***		0.79		1.13	−0.10		0.68		0.83	2.42***		2.43*		2.20+	0.36		2.70*		2.83*
Hispanic	−0.06		1.66*		1.77*	−0.75+		0.50		0.75	2.53***		2.28*		1.70+	0.64		2.26*		2.47*
Other	−1.32		0.13		0.15	0.61		1.65		1.49	0.31		0.08		0.15	0.47		1.34		1.24
Father's R/E (Ref=NH white)																				
NH black		−3.58***	−4.23***		−3.43***		−0.50	−1.07		−0.30		2.11***	0.02		−0.31		−0.71	−3.02*		−2.74+
Hispanic		−0.87	−2.28**		−1.09		−1.25*	−1.64*		−0.51		2.20**	0.31		−0.12		−0.60	−2.51*		−1.94
Other		−0.71	−1.52+		−0.70		−1.73**	−2.24**		−1.45+		1.86*	0.64		0.38		1.08	−0.45		−0.14
Not reported		−4.40***	−5.24***		−2.78*		−1.14	−1.45		0.20		1.00	−0.18		0.93		−2.00+	−3.32**		−2.36
Education (Ref=16 years)																				
1–12 years				−1.45+	−1.58+				−1.12	−1.16				1.04	0.53				−1.13	−1.27
13–15 years				−2.60**	−2.10*				−0.38	−0.47				0.38	−0.05				−1.09	−1.13
17+ years				−1.72*	−1.74*				−0.58	−0.57				−0.77	−0.70				−0.26	−0.28
Household income (Ref≥$100 K)																				
≤$25K				−1.96*	−1.19				−0.95	−1.07					0.94	0.14			1.32	1.37
$25–$50K				−2.51**	−1.87+				−1.03	−1.10					−0.85	−1.50			0.95	0.93
$50–$100K				−1.09	−0.89				−0.92	−0.94					0.49	0.18			1.82+	1.78
Constant	52.06***	52.94***	52.82***	54.65***	54.79***	47.95***	48.40***	48.30***	49.51***	49.42***	70.65***	70.83***	70.59***	71.32***	71.01***	54.73***	55.49***	55.24***	54.92***	54.74***
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

Newborn Epigenetic Study, cord blood leucocytes, 2010–2011.

*p<0.05;

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b, beta coefficient; DMR, differentially methylated region; NH, non-Hispanic; R/E, race/ethnicity.

** p<0.01;

*** p<0.001;

+ p<0.1.

Table 5

Race/ethnic and socioeconomic patterning in DNA methylation at DMRs of imprinted genes which show few disparities, standardised coefficients

	MEG3-IG					***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=16 years)																									
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=>$100 K)																									
<$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

Newborn Epigenetic Study, cord blood leucocytes, 2010–2011.

* p<0.05;

** p<0.01;

*** p<0.001;

DMR, differentially methylated region; NH, non-Hispanic; R/E, race/ethnicity.

+ p<0.1.