Biochimica et Biophysica Acta 1846 (2014) 258–262

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Racial/ethnic disparities in human DNA methylation

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ARTICLE INFO

Article history:
Received 10 January 2014
Received in revised form 1 July 2014
Accepted 3 July 2014
Available online 10 July 2014

Keywords:
DNA methylation
Racial/ethnic disparities
Individual susceptibility
Cancer

ABSTRACT

The racial/ethnic disparities in DNA methylation patterns indicate that molecular markers may play a role in determining the individual susceptibility to diseases in different ethnic groups. Racial disparities in DNA methylation patterns have been identified in prostate cancer, breast cancer and colorectal cancer and are related to racial differences in cancer prognosis and survival.

Contents

1. Introduction

DNA methylation is the most studied epigenetic phenomenon and is defined as the addition of a methyl group to the cytosine base within cytosine–guanine dinucleotides (CpGs) in humans. Approximately 80 to 90% of CpGs are methylated, whereas unmethylated CpGs are frequently clustered in CpG islands (CGIs) at the promoter of over half of all genes [1]. When a CGI becomes methylated, the associated promoter is stably silent [2]. DNA methylation is essential for normal development and is associated with genomic imprinting, X-chromosome inactivation and carcinogenesis [3].

DNA methylation is a heritable change in gene expression not encoded by the DNA sequence [4]. Furthermore, the heritability of methylation states and the methylation gain or loss suggests that DNA methylation is adapted for a specific cellular memory function during development [2]. DNA methylation patterns vary in time and space, and the methylation patterns differ between specific cell-types within

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http://dx.doi.org/10.1016/j.bbcan.2014.07.001
0304-419X/

Table 1
Racial/ethnic disparities in DNA methylation of human different tissues.

Resource	Method	Gene	Difference	Race	References
Peripheral blood	Combined bisulfite restriction analysis (COBRA)	*LINE-1*	Caucasians had signifcantly lower levels of methylation than non-Caucasians	480 Caucasians; 15 African-Americans; 8 Hispanics; 2 Asians; 21 Native Americans	[8]
Peripheral blood	Bisulfite pyrosequencing	*LINE-1*	Non-Hispanic blacks and Hispanics had signifcantly lower levels of methylation than non-Hispanic whites	33 non-Hispanic whites; 69 non-Hispanic blacks; 58 Hispanics	[9]
Peripheral blood	[3H]-methyl acceptance assay		African-American women had lower level of DNA methylation than Hispanics and non-Hispanic Caucasians	32 African-Americans; 29 Caucasians; 24 Hispanics	[7]
Umbilical cord blood	Human methylation 27 BeadChip	Autosomal CpGs	African-American newborns had lower levels of methylation than Caucasians	107 African Americans; 94 Caucasians	[3]
Breast tissue	Methylation-specific PCR (MSP)	*CDKN2A* (*p16^{INK4}*)	African-Americans women had lower level of *CDKN2A* promoter methylation than European-Americans	71 European-Americans; 69 African-Americans	[10]
Colorectal mucosa	Bisulfite pyrosequencing	*ESR1*(*Era*) and *SFRP1*	African Americans had lower level of *ESR1* and *SFRP1* promoter methylation than Caucasians and Hispanics.	22 African Americans; 325 Caucasians; 22 Hispanics	[11]
Normal prostate tissue	Bisulfite pyrosequencing	*TIMP3* and *NKX2-5*	African-American men had higher level of *TIMP3* and *NKX2-5* promoter methylation than Caucasians	18 African Americans; 13 Caucasians	[12]
Peripheral blood	Bisulfite pyrosequencing	*OPRM1*	African-Americans had a higher *OPRM1* promoter CpG island mean methylation level than Hispanics and Caucasian	70 African-Americans; 53 Hispanics; 103 Caucasian	[13]
Peripheral blood	Bisulfite pyrosequencing	*VDR*	Yoruba showed significantly higher methylation than Caucasians at several CpG sites in *VDR* promoter CGI 1060	30 Yorubas; 28 Caucasians,	[14]
Lymphoblastoid cell lines from the HapMap project	Illumima Infinium Human Methylation 27 Bead Chip	27, 578 CpG sites	8, 475 CpG sites differed between Caucasians and Yorubas	30 trios (mother/father/offspring) of Yoruban (West African) ancestry; 30 family trios of Northern European ancestry	[6]
Prostate tumor	Real-time methylation-sensitive PCR	*CD44*	African-American men had a higher *CD44* promoter methylation level than Caucasian	47 African-Americans; 64 Caucasians	[17]
Prostate tumor	Real-time methylation-sensitive PCR	*CD44*	African-American men had a higher *CD44* promoter methylation level than Caucasian	41 African-Americans; 49 Caucasians	[16]
Benign prostatic hyperplasia (BPH)	MSP	*PYCARD* (*TMS1/ASC*)	African-American men had a higher *PYCARD* promoter methylation level than Caucasian	12 African-Americans; 22 Caucasians	[19]
Prostate tumor	Bisulfite pyrosequencing	*AR*, *RARβ2*, *SPARC*, *TIMP3*, and *NKX2-5*	African-American men had a higher *AR*, *RARβ2*, *SPARC*, *TIMP3*, and *NKX2-5* promoter methylation levels than Caucasians	18 African Americans; 13 Caucasians	[12]
Prostate tumor	MSP	*RARB* and *APC*	African-American men had a higher *RARB* and *APC* promoter methylation levels than Caucasians	211 African Americans; 300 Caucasians	[20]
Breast tumor	Bisulfite pyrosequencing	*CDH13*	African-American women had a higher *CDH13* promoter methylation level than European-Americans	32 African-Americans; 33 European-Americans	[24]
Breast tumors	MSP	*SCGB3A1*(*HIN-1*), *TWIST1* (*Twist*), *CCND2* (*Cyclin D2*), and *RASSF1* (*RASSF1A*)	Age <50 African-American women had a higher promoter methylation levels of *SCGB3A1*, *TWIST1*, *CCND2*, and *RASSF1* than age <50 Caucasians	67 African Americans; 44 Caucasians	[23]
Normal colonic tissue from individuals with and without a histologically-confirmed adenoma	Bisulfite pyrosequencing	*LINE-1*	Hispanics had higher levels of *LINE-1* methylation than African Americans and Caucasians	388 individuals including Hispanics, African Americans and Caucasians	[29]
Colorectal cancer	MSP	*GPNMB*, *ICAM5*, and *CHD5*	African-Americans had a higher *GPNMB*, *ICAM5*, and *CHD5* promoter methylation levels than Iranians	51 Iranians; 51 African Americans	[26]
Non-small cell lung cancer	MSP	*MGMT* and *GSTP1*	The methylation rates of *MGMT* and *GSTP1* were significantly higher in the 196 USA and Australian cases than in those from 288 Japan and Taiwan	196 USA and Australian cases; 288 Japan and Taiwan cases	[31]
Malignant pleural mesothelioma	MSP	*GDF10* (*BMP3b*)	Americans had lower level of *GDF10* promoter methylation than Japanese	17 Japanese; 40 Americans	[32]
Malignant mesothelioma	MSP	*IGFBP3*	Americans had lower level of *IGFBP3* promoter methylation than Japanese	16 Japanese; 40 Americans	[33]
Endometrial carcinoma	Southern blot analysis of HpaII-digested DNA	Ribosomal DNA (rDNA)	African American women had lower level of rDNA methylation than Caucasians	39 African Americans; 176 Caucasians	[36]
Neuroblastomas	MSP	*HOXA9*	Germans had lower level of *HOXA9* promoter methylation than Japanese	140 Japanese; 153 Germans	[35]

a single organ [5]. For example, genomic DNA hypomethylation is associated with aging, and gene-specific promoter DNA hypermethylation occurs in a tissue-specific manner. Moreover, established epigenetic patterns during the fetal period can change during adulthood because of environmental factors [6,7].

Various racial groups differ in their DNA methylation patterns in both healthy and unhealthy tissue [3,8]. There is evidence that in different racial groups, DNA methylation in cancerous tissues or changes in DNA methylation occur during oncogenesis [3]. Endogenous and exogenous factors may influence epigenetic changes throughout life; therefore, epigenetics plays a role at the interface between the environment and the genome, and the environment may act to alter cancer susceptibility through DNA methylation [3,5,7,9].

2. Racial/ethnic disparities in the DNA methylation patterns of healthy individuals

In a cancer-free population, the global genomic methylation of leukocyte DNA was different among various racial groups (Table 1). Hsiung et al. studied 526 healthy individuals who were controls in a case–control study of head and neck squamous cell carcinoma and found a 1.26% significantly higher level of leukocyte *LINE-1* methylation in non-Caucasians compared to Caucasians [10]. By contrast, Zhang et al. observed 2.2% lower global DNA methylation levels as determined by the pyrosequencing of *LINE-1s* in non-Hispanic blacks, and a 1.3% lower level of leukocyte *LINE-1* methylation in Hispanics compared to non-Hispanic whites [11]. In normal cells, the majority of the *LINE-1* loci are hypermethylated or partially methylated, and few *LINE-1* loci are hypomethylated [12]. Among healthy middle-aged women, African-Americans (AAs) had lower global levels of DNA methylation relative to Caucasians or Hispanics [9]. Although the DNA methylation patterns differ between children and adults, racial differences remain in children. Adkins et al. found that 13.7% of the autosomal CpGs in newborns exhibited significantly different levels of DNA methylation between AAs and Caucasians, and AA newborns had lower levels of methylation, consistent with the results of Zhang. After the Human Methylation 27 BeadChip was analyzed, the KEGG pathways enriched for the loci with significant associations with race and DNA methylation included four cancer pathways, pancreatic, prostate, bladder and melanoma, with substantial differences in incidence between the races, which were highly represented among the genes containing significant race-divergent CpGs [3].

Additionally, for breast tissue and colorectal mucosa, several genes in AAs were hypomethylated relative to Caucasians in a cancer-free population. Although hypermethylation of the tumor suppressor gene *CDKN2A* (*$p16^{INK4}$*) promoter occurs in breast tumors, hypermethylation also appears in both preinvasive breast lesions and breast tissues from apparently healthy women. *CDKN2A* hypermethylation in breast tissues from healthy women was present in 28% of AA women, whereas it was detected in 65% of European-American women [13]. *ESR1* (*Era*) and *SFRP1* are associated with regulating growth, differentiation and tumorigenesis in the colon. AAs had significantly lower levels of *ESR1* and *SFRP1* promoter methylation in normal colorectal mucosa than Caucasians and Hispanics [14].

However, significantly higher levels of methylation for *NKX2-5* and *TIMP3* were detected in normal prostate tissue samples from AAs compared to Caucasians [15]. The methylation level of the *OPRM1* promoter CpG island in the controls of a heroin addict case–control study was compared, and African-Americans had a higher mean methylation level (19.6%) of peripheral blood lymphocytes than the Hispanics (16.1%) and Caucasians (17.4%) [16]. *VDR* promoter methylation was screened by bisulfite pyrosequencing in a case–control study of tuberculosis (TB); however, there was no difference in the *VDR* promoter CGI 1060 regional methylation between TB cases and controls, and the mean site-specific methylation was significantly higher in Yorubas at CpGs 2, 5, 7, 8, 10, 13, and 14, and significantly lower at CpGs 4 and 6 compared to Caucasians [17].

A non-parametric Wilcoxon test was performed to identify CpG sites differing in methylation between Caucasians and Yorubas in 180 cell lines derived from one African and one European population, and 8,475 sites differed between the populations. These population-level differences were small, with only 1,033 sites (3.9%) differing by an average of over 10% methylation, and 3,695 sites (14.0%) differing by over 5%. Possibly because of their small magnitudes, the differences in DNA methylation did not explain the variation in gene expression levels between the different races, but racial disparities in DNA methylation patterns occurred in healthy individuals [8].

3. Racial/ethnic disparities in the DNA methylation level of prostate cancer

In the United Sates, the incidence and mortality of prostate cancer (PC) are approximately 2-fold higher among AAs than Caucasians and are very low in Asians [18]. Two studies by Woodson et al. [19,20] examined racial differences in the methylation status of the *GSTP1*, *CD44*, *E-cadherin*, *RASSF1*, *RARb 2*, *EDNRB*, *Annexin-2*, and *CAV1* genes in prostate tumors and observed only a slightly higher frequency of *CD44* methylation among AAs relative to Caucasians. Comparison of *GSTP1* methylation in prostate cancer samples with their clinical and pathological outcomes showed that AAs with *GSTP1* methylation are 13.3 times more likely to have PC, whereas in Caucasians, this ratio is only 3.8 [21]. These results suggest that *GSTP1* hypermethylation is a sensitive diagnostic marker for AAs [18]. By contrast, Das et al. [22] observed that the *CD44* and *GSTP1* were not significantly different for methylation between populations, but there was a significantly higher methylation frequency for *PYCARD* (*TMS1/ASC*) in benign prostatic hyperplasia (BPH) for AAs. Higher *AR*, *RARβ2*, *SPARC*, *TIMP3*, *NKX2-5*, *RARB* and *APC* promoter methylation levels were also observed for AAs compared to Caucasians, whereas *GSTP1* hypermethylation did not occur in AAs [22,23]. Although these data may be contradictory, studies in this area may be useful for understanding the molecular basis of race-related disease, as well as in identifying biomarkers to better detect and assess prostate cancer in a particular ethnic group.

4. Racial/ethnic disparities in the DNA methylation level of breast cancer

In the United States, AA women are more likely to develop aggressive breast tumors than Caucasians [24]. Environmental factors that change the methylation patterns may partially explain the difference. The Illumina GoldenGate methylation bead arrays were used to analyze 117 Caucasian, 13 African American, 10 Hispanic and 10 Asian breast cancer cases. The results showed that the patient race was significantly associated with methylation class membership, with the majority of AAs (54%) in class 2, and 40% of Hispanic cases in class 4 [25]. Hormone receptor-negative tumors from young AA patients show distinct DNA hypermethylation at *SCGB3A1* (*HIN-1*), *TWIST1* (*Twist*), *CCND2* (*Cyclin D2*), and *RASSF1* (*RASSF1A*) compared to European-Americans (EA) tumors, suggesting candidate tumor biological differences between the two racial groups as they relate to cancer epigenetics [26]. When the promoter methylation levels of seven tumor markers candidate genes, *CDKN2A*, *ESR1*, *RASSF1*, *RARβ2*, *CDH13*, *SCGB3A1*, and *SFRP1*, were analyzed and the global methylation level was determined for *LINE-1* in breast tumors, a higher level of *CDH13* promoter methylation was detected for AA women than EA women. Therefore, *CDH13* hypermethylation may contribute to the distinct molecular alterations hypothesized for AA and EA tumors that possibly play a role during the early onset of breast cancer [27].

5. Racial/ethnic disparities in the DNA methylation level of colorectal cancer

In Israel, the rate of colorectal cancer (CRC) differs significantly among the different ethnic groups. The incidence is highest in Ashkenazi Jews (European- and American-born Jews), intermediate in Sephardic Jews (Asian- and African-born Jews), and lowest in Israeli-born Jews [28]. African-Americans had higher *GPNMB*, *ICAM5*, and *CHD5* promoter methylation levels than Iranians [29]; however, there was no difference in methylation of the *MLH1* promoter between Jews and Israeli-born Arabs [30]. Although the prevalence of CRC differs among different ethnic groups within the United States where AAs have a 10% higher incidence of CRC than Caucasians, the incidence is the opposite for Israel [31]. A higher level of global methylation was observed among Hispanics and other racial groups compared to AA and Caucasians, and no difference in methylation levels in normal colonic tissue was observed from individuals with and without a histologically confirmed adenoma [32]. Racial disparities have been observed in colorectal cancer and this may partially explain the difference in incidence and aggressiveness of CRC in various racial groups.

6. Racial/ethnic disparities in the DNA methylation level of lung cancer

Johanning et al. [33] developed an immunohistochemical assay that uses a monoclonal antibody to specifically bind to 5-methyl-2′-deoxycytidine (5-mC) to assess the global DNA methylation in lung squamous cell carcinomas (SCCs), and the results suggested that global DNA hypomethylation is associated with the development of SCCs in Caucasians but not AAs. In the associated uninvolved bronchial mucosa and epithelial hyperplasia of 53 Caucasians and 23 AA, the 5-mC scores of SCC were significantly lower than in the uninvolved bronchial mucosa (UBM) and epithelial hyperplasia (EH) in Caucasians. In AAs, however, the 5-mC staining of SCC was not significantly different from those of the UBM or EH. The methylation rates of the two genes *MGMT* and *GSTP1* were significantly higher in the 196 US and Australian cases (15% for *MGMT* and *GSTP1*) than in the 288 cases from Japan and Taiwan (1% for *MGMT* and *GSTP1*) [34]. These results may reflect racial differences in lung carcinogenesis or molecular pathogenesis.

7. Racial/ethnic disparities in DNA methylation level of malignant mesothelioma

For malignant mesothelioma (MM), the methylation status of MM in Japanese patients was significantly higher than in US patients, suggesting that geographic differences in the *IGFBP3* and *GDF10* (*BMP3b*) might be influenced by ethnic or pathogenic differences, despite no evidence to support the hypothesis that the incidence of MM differs among different racial groups [35,36].

8. Racial/ethnic disparities in the DNA methylation level of other tissues and cancers

The racial/ethnic differences in clinical and biologic risk factors and outcomes of patients with neuroblastoma (NBL) were observed [37]. This difference may be partially explained by the DNA methylation differences among different racial groups. For example, German NBL patients had lower levels of *HOXA9* promoter methylation than Japanese NBL patients [38]. In endometrial carcinoma, rDNA methylation differences occurred between African-American female patients and Caucasian patients. Because rDNA methylation is possible a marker for aberrant methylation involving key growth-regulatory genes, epidemiologic studies have shown that African-American female patients are twice as likely as Caucasian patients to die from endometrial carcinoma; therefore, the differences in rDNA methylation may reflect underlying factors that contribute to the observed racial differences in outcome [39].

9. Possible factors contributing to racial/ethnic disparities in DNA methylation

These studies discussed above suggest that DNA methylation is divergent between populations and that this divergence may be due in large part to a combination of differences in allele frequencies and complex epistasis or interactions between the gene and environment [8]. Although DNA methylation is a stable epigenetic mark, numerous environmental factors, including nutrition, exposure to environmental pollutants, and social environment conditions, have been associated with variations in DNA methylation [3]. Both shared and non-shared environments can trigger methylation changes, and this may have evolutionary consequences, even in the absence of sequence variation [7,40]. Evidence suggests that DNA methylation may be altered by the dietary availability of methyl groups. Folate, in the form of 5-methyltetrahydrofolate (MTHF), is involved in the remethylation of homocysteine (Hcy) to methionine, the precursor of S-adenosylmethionine (SAM), which is the primary methyl donor for the majority of biological methylation reactions [32]. It is this plasticity that underlies much of the potential contribution of DNA methylation to multi-factorial diseases, complex phenotypes and racial disparity [3].

10. Limitations of the present study

There are several limitations of these studies that should be noted. First, bisulfite sequencing is currently the gold standard for DNA methylation analysis in cancer, but this assay was not performed in some studies [41,42]. Second, a vast majority of studies in Table 1 have small sample sizes. Ioannidis [43] summarized several corollaries, one of which is that the smaller the study conducted in a scientific field, the less likely the research findings are to be true. Therefore, researchers should design better studies and increase the sample size. Third, if a particular human disease process is caused by the dysfunction of either a specific cell-type or multiple cell-types, then the optimal approach is to analyze the molecular changes in the afflicted cell-types specific to the disease process [5]. Although many epigenetic studies rely on peripheral blood leukocytes as a surrogate for alterations in tumor cells, there is very little evidence supporting the validity of inferring epigenetic mechanisms of non-hematologic disorders from the epigenetic analysis of blood leukocytes [5].

Acknowledgements

This study was supported by the Chongqing Key Laboratory of Birth Defects and Reproductive Health Fund (No.0901), the Natural Science Foundation Project of CQ CSTC (2009BA5082, 2012jjA10070), the Science-Technology Research Program of the CQ Municipal Commission of Education (KJ120326, KJ1400231), the Science-Technology Three Items Project of CQ Yuzhong District (No.20130126) and the CQMU Public Health School Fund (No.Gwzk201301).

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