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*Review Article*

# A compendium of population wide DNA methylation profile for oral cancer in India

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## ABSTRACT

With the emergence of epigenetics, constant attempts are been made to decipher the molecular mechanisms in carcinogenesis. Epigenetic modifications, especially the DNA methylation, have been perceived in oral squamous cell carcinoma (OSCC). The target genes differentially methylated in OSCC still largely remains unknown. There are differences in the molecular alterations in OSCC, regarding geographic location. Therefore, the aim of this review is to present status-quo of existing studies on Indian population to better understand the aberrant patterns of DNA methylation in OSCC that could serve as potential prognostic and diagnostic biomarkers to improve therapy and extend overall survival. The literature was searched using MEDLINE/PubMed, Wiley, Google Scholar, and Science Direct to identify and include most of the relevant articles published from the year 2000 till date in English language. The review would prove to be a valuable resource for population specific investigations and detecting novel biomarkers for OSCC.

**Keywords:** DNA methylation, Epigenetics, Oral squamous cell carcinoma, Hypermethylation, Hypomethylation

## INTRODUCTION

Recently, non-communicable diseases are on surge as they have prevailed beyond our capacity to control it. They are the major cause of preventable deaths and disability. Among these, the most common being cancer has posed a challenge to mankind since its inception. Today, cancer is second major cause of death (first being cardiovascular disease). GLOBOCAN (global cancer incidence, mortality, and prevalence) database, an initiative of International Agency for Research on Cancer is a cancer organization of the World Health Organization; in 2018 reported that worldwide cancer have escalated to 18.1 million new cases and 9.6 million cancer deaths.[1] They have anticipated that by 2040, the global cancer burden to reach 29.5 million new incident cases and 16.3 million deaths.[2] In the past few years, the role of "epigenetic phenomenon" has emerged significantly. DNA methylation is stable and robust epigenetic marker that often occurs early in cancer development. The genes targeted in oral squamous cell carcinoma (OSCC) still largely remain unknown. So far, no global profile of CpG Island (CGIs) methylation in OSCCs has yet emerged, due to limited samples with few genes being analyzed in the previous studies. Therefore, this comprehensive critical review was conducted to better understand the current status of evidence on DNA methylation patterns in Indian population that may provide insight into the identification of significantly differentially methylated loci/probes (DMPs). This

compiled data on target genes affected in specific region of specific population summarizes the significance of epigenetic landscape of OSCC in translational research to achieve early diagnostic and therapeutic landmark. The literature was searched using MEDLINE/PubMed, Wiley, Google Scholar, and Science Direct to identify and include most of the relevant articles published from the year 2000 till date.

## ORAL CANCER BURDEN

Oral cancer is a leading public health concern in South Central and Southeast countries of Asia. India has one-third of oral cancer cases of the world and therefore has long been regarded as an epicenter of oral cancer.[3]

It accounts for around 30% of all cancers primarily related to tobacco as reported by the Indian Council of Medical Research. According to GLOBOCAN 2018, new cases of oral cancer in India is estimated to rise from 1.15 million in 2018 to 1.9 million by 2040 and oral cancer deaths is estimated to rise from 0.78 million to 1.33 million by 2040.[2,4] Cancers of lip oral cavity are the leading cause of cancer incidence (16.1%) and mortality (12.3%) in males. The data from National Cancer Registry Programme (Population-Based Cancer Registries) showed highest age-adjusted rate for oral cancer (18.11) in males of Ahmedabad urban, followed by Bhopal (14.2).[5] Among females, it is 4$^{th}$ most common cancer with incidence of 4.8% and mortality 5.9%. Despite easy accessibility to oral cavity, an exponential rise in oral cancer can be attributed to diagnosis at later stages, disparities in access to quality health services and high exposure to risk factors such as tobacco due to easy affordability.[6]

Oral cancer is a multistage, multistep, and multifactorial process. OSCC is the most common oral cavity cancer in Indian subcontinent as compared to developed countries. The risk factors can be broadly classified into two groups – environmental (or modifiable) and genetic (or unmodifiable).[7] The prominent risk factors implicated in oral cancer are tobacco (smoked or smokeless), betel nut/areca nut, alcohol, human papilloma virus (HPV), exposure to carcinogens (physical, chemical, and biological), diet, and lifestyle. Since long time, environmental and genetic factors were considered to be independent mechanisms, but recent evidence suggests that epigenetics bridges these two factors.[8] However, the genetic and epigenetic mechanisms are distinct but quite closely related. Epigenetic changes depend on modification of DNA unlike genetic changes which depend on DNA sequence change. Genetic changes are stable and irreversible, whereas epigenetic changes are often reversible. The genotype is constant whereas the epigenetic process is dynamic and often changes in response to diseases and environmental factors.[8] Genetic changes usually involve a single gene whereas epigenetics involve more than one gene.[9] Although our epigenetic makeup is more stable during adulthood, it is still thought to be modifiable by lifestyle choices and environmental influence.

## EPIGENETIC LANDSCAPE

Conrad Waddington in 1942 first coined the term "Epigenetics."[10] The word "epi" in Greek means "upon" or "above" or "on top of" genetics. It turns genes "on" or "off." These external modifications in DNA does not change its sequence but affects how cells "read" genes.[11-13] Since its recognition, the description modified over time and with consensus in 2008 it is now defined as "stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence."[14] In addition, epigenetic modifications are transient and potentially reversible. At present, three major epigenetic mechanisms are known – DNA methylation, histone modification, and non-coding RNA -associated gene silencing.

## DNA METHYLATION

DNA methylation is perhaps the most common and best studied mechanism. Griffith and Mahler in 1969 first suggested an important biological role of DNA methylation or demethylation.[9] It is covalent addition of a methyl group to the 5-carbon position of cytosine bases that are located 5' to a guanine base separated by a phosphate molecule in a CpG dinucleotide. These CpG dinucleotides are asymmetrically scattered throughout the genome but are usually found clustered in 0.5–4 kb regions and hence named CGIs.[15] Approximately 50% of genes show presence of CGIs in their promoter regions and methylation mostly occurs in these promoter regions or the first exon sequence.[16] DNA methylation is mediated by different DNA methyltransferases (DNMT), a family of enzymes with potential to transfer methyl group to target DNA by usually involving lysine and arginine residues on histone tails.[10] DNA methylation plays a significant role in regulating gene expression and chromatin architecture.[8] Aberrant methylation patterns have been documented in various cancers. The first being genome-wide hypomethylation of CGIs and the other is hypermethylation of CGIs.

### Hypomethylation

Global DNA hypomethylation occurs in repeat sequences, gene deserts, transposons, or CpG dinucleotides located in introns. It causes genome instability, loss of imprinting, and abnormal chromosomal structures. It may also stimulate activation of latent viruses and oncogenes.[16,17]

### Hypermethylation

In normal cells with transcriptionally active genes, CGIs are poorly methylated.[17] The highly methylated CGIs in

the promoters of genes lead to transcriptional silencing of tumor suppressor genes and thus promotes malignant transformation.[16] Neoplastic cells may simultaneously harbor regional areas of hypermethylation, widespread (global) genomic hypomethylation, and increased DNA-methyltransferase (Dnmt) activity.

## DNA METHYLATION PROFILE IN OSCC PATIENTS IN INDIA

OSCC in Indian population has different molecular mechanisms as compared to American and European population, possibly due to differences in environmental and risk factors.[18] The key characteristics of reviewed studies are summarized in Table 1.[19-36] The studies included different sets of population across the states of India. There is heterogeneity among the studies regarding type of sample, sample size, control sampling, socio-economic, and lifestyle (e.g., gutkha, tobacco, and alcohol) characteristics and methylation percent, with less emphasis on data from controls. Over the past two decades, there have been major developments in the methodologies to examine elusive epigenome. With the advent of these molecular techniques, DNA methylation can be examined both at locus-specific context and genome wide. Thirteen studies analyzed methylation patterns using a methylation specific PCR technique (MSP), three studies used methylation sensitive restriction analysis, one study used RT-PCR, and one study used differential methylation hybridization microarray and validated by bisulfite genome sequencing. It is evident from our review that initial studies emphasized more on locus-specific methylation analysis whereas with the evolving molecular techniques, the recent studies focused more on genome wide methylation enabling identification of various differentially methylated sites and genes [Table 2]. For methylation analysis, majority of the studies used biopsy-confirmed tissue samples. Most of the reviewed studies included paired control samples from the same individual adjacent to the tumor tissue to reduce the potential confounding bias. Notably, saliva,[18] scrape,[19] and blood[18,20-24] were also used for analysis. Recently, the use of whole blood and saliva in methylation studies has become common as potential non-invasive mediums for investigation.

It is clearly evident that majority of studies reported hypermethylation of the CpG sites than hypomethylation. Table 3 summarizes data on differentially methylated CpG sites. DNA hypomethylation remains less studied as compared to hypermethylation due to its unclear role in carcinogenesis. DNA hypomethylation in cancer is often seen in arthrobacter luteus repeats, satellite DNAs, and long interspersed nuclear elements, etc., mostly in repetitive regions, randomly spread over the genome.[25] These DNA repeats comprise nearly half of the genome. Therefore, DNA hypomethylation is generally considered a global phenomenon not suitable for use as a biomarker. The differential methylation pattern across the CGIs, shores and shelves suggested different mechanisms of hypo- and hypermethylation in OSCC development.[26,27] Das *et al*. reported considerable variation in proportion of DMPs across the chromosomes. It was found to be highest for chromosome 8 and lowest for chromosome 16. The proportion of hypermethylated DMPs was higher than hypomethylated DMPs in all chromosomes except chromosome 8 and 21.[28] Some of the main genes that are differentially methylated in OSCC are those involved in diverse pathways such as regulation of the cell cycle, physiological signaling and metabolism, proliferation, DNA repair, and apoptosis.[23,28] The ingenuity pathway analysis performed by Basu *et al*. showed canonical pathways of IL9 signaling and CTLA4 signaling in cytotoxic T lymphocytes to be significantly enriched.[26] Pathway enrichment analysis by Das *et al*. identified five significantly enriched KEGG pathways (PPAR signaling, arachidonic acid metabolism, B cell receptor signaling pathway, longevity regulating pathway, and genes associated with acute myeloid leukemia) and 22 GO terms (pathways related to G0 to G1 transition, apoptosis, chemokine-mediated signaling pathway, interferon signaling pathway, and various immune-related processes).[28]

Few loci involved in the cell cycle control (p16, p14), DNA repair (MGMT) and apoptosis (DAPK) have been reported consistently in multiple studies and thus appear to be significant markers of choice for further evaluation. A closer look at the current evidences revealed hypomethylation to occur at promoters of genes mainly involved in immune response pathways that induced an anti-tumor T cell response leading to mobilization of T lymphocytes in the neoplastic environment.[26] Genes encoding T lymphocyte regulation such as CD28, CD80, CD86, ZAP70, PI3 kinase, or the PTPN22 tyrosine phosphatase and CTLA4 involved in negatively regulating cytotoxic T cell signaling, are hypomethylated and overexpressed in the neoplastic environment.[27] Kaur *et al*. associated p16 hypermethylation with nodal involvement and hence poor outcome.[18] Alyasiri *et al*. indicated *PTEN* promoter hypermethylation to be more frequent in poorly differentiated OSCC among the Indian population.[21] *LATS2* gene promoter hypermethylation was statistically significant in tobacco chewers and smokers.[24] Comparative analysis with the TCGA-HNSCC data revealed 94.6% similarities by Basu *et al*. and 80.4% similarities by Das *et al*.[26,28] Khongsti *et al*. found approximately 29.54% similarities in hypermethylated genes of promoter region. Among 38 genes hypermethylated in promoter region reported by them, 14 genes were similar to TCGA-HNSCC study.[27] Kaplan–Meier survival analysis of TCGA-HNSCC

**Table 1:** Characteristics of the reviewed studies (*n*=18).

| N | Author | Year | Parts of India | Cases | Controls | Sample analyzed | Technique | Loci examined |
|---|---|---|---|---|---|---|---|---|
| 1. | Viswanathan *et al*.[30] | 2003 | South | 99<br>51(p15) | 25 A | Tissue | MSRA | p16, p15, hMLH1, MGMT, E-cad |
| 2. | Kulkarni *et al*.[19] | 2004 | West | 60 | 60A<br>20 normal mucosa scraping | Tissue, Scrape | MSP | p16, DAPK, MGMT GSTP1 |
| 3. | Ghosh *et al*.[31] | 2009 | East | 40 dysplastic lesion<br>63 HNSCC | 40 A<br>63 A | Tissue | MSRA | SH3GL2, p14, p15, p16 |
| 4. | Kaur *et al*.[18] | 2010 | North | 92 OSCC | 48 A<br>30 saliva and sera | Tissue, Saliva, Sera | QMSP | DCC, EDNRB, p16INK4a and KIF1A |
| 5. | Alyasiri *et al*.[21] | 2013 | North | 100 | 100A<br>Blood | Tissue blood control | MSP | PTEN |
| 6. | Bhatia *et al*.[20] | 2014 | North | 76 OSCC<br>54 premalignant | 16 H | Tissue, blood | MSP | MGMT, p16 |
| 7. | Asokan *et al*.[32] | 2014 | South | 10 leukoplakia<br>10 OSCC | 5 H | Tissue | MSP | p16, p15, hMLH, MGMT, E-cad |
| 8. | Choudhury *et al*.[33] | 2015 | NE | 71 | 45 A | Tissue | MSP | p16, DAPK, RASSF1, BRAC1, GSTP1, ECAD, MLH1, MINT1, MINT2 and MINT31 |
| 9. | Sushma *et al*.[34] | 2015 | South | 50 | 50 A | Tissue | MSP | PTEN, p16 |
| 10. | Balasubramanian *et al*.[35] | 2015 | South | 23 | | Tissue | MSRA | BRD7 |
| 11. | Krishnan *et al*.[22] | 2016 | South | 52 OTSCC | 52 A | Tissue and/ blood | MSP | Whole genome |
| 12. | Basu *et al*.[26] | 2017 | East | 64 WDSCC | 64 A | Tissue | MSP | Whole genome |
| 13. | Jha *et al*.[23] | 2017 | North | 40 | 20 H | Blood | MSP | FHIT, P14 |
| 14. | Bhat *et al*.[29] | 2017 | South | SCCT | | | DMH validated by BGS | *LRPPRC*, *RAB6C*, *ZNF471* |
| 15. | Khongsti *et al*.[27] | 2018 | NE | 12 | 12 A | Tissue | MSP | Whole genome |
| 16. | Das *et al*.[28] | 2019 | West, East | 101 OSCC GB | 101 A | Tissue | MSP | Whole genome |
| 17. | Khongsti *et al*.[36] | 2019 | NE | 17 | 17 A (2cm away) | Tissue | RT-PCR | FLT3, EPB41L3, SFN |
| 18. | Goel *et al*.[24] | 2020 | North | 70 | 20 H blood | Tissue, blood, serum | MSP | LATS2 |

A: Autologous (control from HNSCC themselves), H: Heterogeneous (control from other individuals), NE: Northeast, MSP: Methylation-specific polymerase chain reaction, QMSP: Real-time quantitative MSP, MSRA: PCR-based methylation-sensitive restriction analysis, Pyro: Pyrosequencing, DMH: Differential methylation hybridization microarray and validated by bisulfite genome sequencing (BGS), OTSCC: Oral tongue squamous cell carcinoma, WDSCC: Well differentiated squamous cell carcinoma, GB: Gingivobuccal sulcus

expression data revealed patients with low expressions of *DAPK1*, *RAB6C*, and *ZNF471* to have poorer survival than patients with high expression ($P = 0.02$).[29] The epigenome wide methylation analysis identified several novel genes [Table 4]. The functional significance of these novel genes needs to be characterized.

Interestingly, epigenetic alterations in certain cancer genes can be altered by known drugs. The drugs that are known to induce reversal of expressions of such genes include dasatinib, tamoxifen, aspirin, and calcitriol. CD274, CD80, TET1, DNMT3B, PPARG, and PIK3CD gene expressions were altered by these drugs.[28] Although our review revealed

**Table 2:** Whole genome-wide methylation analysis of OSCC patients.

| N | Author (year) | CpG sites/ probes (DMP) | CpG regions/ genes (DMR) | Hypermethylated genes | Hypomethylated genes |
|---|---|---|---|---|---|
| 1 | Krishnan *et al*. (2016)[22] | 485,512 | | 27,276 | 21,231 |
| 2 | Basu *et al*. (2017)[26] | 21,810 | | 5670 | 16,140 |
| 3 | Bhat *et al*. (2017)[29] | | | 241 | 116 |
| 4 | Khongsti *et al*. (2018)[27] | 27,205 | 3811 | 38 | 7 |
| 5 | Das *et al*. (2019) [28] | 25,321 | | 11,522 | 8501 |

DMP/S: Differentially methylated probes/sites, DMR/G: Differentially methylated regions/genes

**Table 3:** Summary list of differentially methylated genes (both hyper- and hypo-methylated).

| N | Author | Year | Loci examined | Methylation pattern |
|---|---|---|---|---|
| 1. | Viswanathan *et al*.[30] | 2003 | p16, p15, hMLH1, MGMT, E-cad | Hypermethylated |
| 2. | Kulkarni *et al*.[19] | 2004 | p16, DAPK, MGMT | Hypermethylated |
| 3. | Ghosh *et al*.[31] | 2009 | SH3GL2, p14, p15, p16 | Hypermethylated |
| 4. | Kaur *et al*.[18] | 2010 | DCC, EDNRB, p16INK4a and KIF1A | Hypermethylated |
| 5. | Alyasiri *et al*.[21] | 2013 | PTEN | Hypermethylated |
| 6. | Bhatia *et al*.[20] | 2014 | MGMT, p16 | Hypermethylated |
| 7. | Asokan *et al*.[32] | 2014 | p16, p15, hMLH, MGMT, E-cad | Hypermethylated |
| 8. | Choudhury *et al*.[33] | 2015 | p16, DAPK, ECAD, RASSF1, MINT1, MINT2 and MINT31 | Hypermethylated |
| 9. | Sushma *et al*.[34] | 2015 | PTEN, p16 | Hypermethylated |
| 10. | Balasubramanian *et al*.[35] | 2015 | BRD7 | Hypermethylated |
| 11. | Krishnan *et al*.[22] | 2016 | UBE4B, CCDC13, LRP5L, BCL3, MIR4260, FOXK2, and COL18A1<br>GSTM2 | Hypermethylated<br>Hypomethylated |
| 12. | Basu *et al*.[26] | 2017 | LXN, ZNF154, ZNF577, ZSCAN31, CTDSP1, LDLRAD4, and HLA-DPB1<br>PTPN22, RUNX1, IL6, CD28, TLR1, CD80, CD22, and TNFa<br>CD86, CTLA4 | Hypermethylated<br>Hypomethylated |
| 13. | Jha *et al*.[23] | 2017 | FHIT, P14 | Hypermethylated |
| 14. | Bhat *et al*.[29] | 2017 | LRPPRC, RAB6C, and ZNF471 | Hypermethylated |
| 15. | Khongsti *et al*.[27] | 2018 | ADPRH, AOX1, BVES, C17orf107, C3orf62, CHAD, CKMT2, CLDN11, CPXM1, EPB41L3, FAM184B, FLT3, FUZ, GFRA1, GPR81, HOXA4, HOXB1, KCNC3, KHDRBS2, LRAT, MED12L, MME, NEFH, NELL1, NID2, NDY, NRIP2, RUNDC3B, SLC35F1, SNAP91, SYT9, THSD7A, VSX1, WT1, ZNF154, ZNF583, ZSCAN16<br>DAPP1, DNAH1, FCRL3, KRT6A, LAMB3, SFN, TM4SF19, TMEM132B | Hypermethylated<br>Hypomethylated |
| 16. | Das *et al*.[28] | 2019 | ZNF132, ZNF626, ZSCAN18, ZNF844 ZNF829, ZNF880, and ZNF229<br>SH2D2A, PHYHD1, and IGF2BP2<br>CD274, CD80, CD86, DNMT3B | Hypermethylated<br><br>Hypomethylated |
| 17. | Khongsti *et al*.[36] | 2019 | FLT3, EPB41L3<br>SFN | Hypermethylated<br>Hypomethylated |
| 18. | Goel *et al*.[24] | 2020 | LATS2 | Hypermethylated |

some promising cues, some of the studies were subject to limitations in terms of non-uniformity in sampling technique especially control samples. Many hypermethylated loci were reported but it lacked validation. However, the recent genome-wide methylation studies included the validation cohort. Clonal validation by Basu *et al*. showed hypermethylation in promoter regions of HLA-DPB1 (12–81%), LHX1 (34–98%), LXN (2–29%), and LDLRAD4 (0–38%), and hypomethylation of PTPN22 (30–86%) in tumors compared to adjacent normal tissues.[26] WT1, a candidate gene selected by Khongsti *et al*. for validation and confirmation experiment clearly showed a significant difference in levels of DNA methylation between the tumor and adjacent normal tissue.[27]

**Table 4:** List of reported novel genes.

| N | Author | Year | Novel genes |
|---|---|---|---|
| 1. | Basu *et al*.[26] | 2017 | LXN, ZNF154, ZNF577, CTDSP1, RUNX1, CD28, CD80 |
| 2. | Khongsti *et al*.[27] | 2018 | ZSCAN16, MED12L, FAM184B, DNAH11 |
| 3. | Das *et al*.[28] | 2019 | DNMT3B and TET1 |

## CONCLUSION

There has been general concensus that DNA hypermethylation and hypomethylation patterns are controlled by specific sets of epigenetic genes acting independently but functions simultaneously in different parts of genome. Whole genome screening has identified DNA hypermethylation in promoter region of tumor suppressor genes and global DNA hypomethylation of oncogenes to play crucial role in OSCC. A deeper insight into methylation status of reported "novel genes" with regard to their functional attributes may significantly help to understand oral carcinogenesis. There is an urgent need of population specific approaches to achieve therapeutic and diagnostic milestones that could be applied across geographic locations with success.

This study is relatively the first-ever to present extensive data of Indian population on differentially methylated genes in OSCC that can serve as novel potential DNA methylation biomarker.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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