# CHROMOSOMAL ALTERATIONS AND GENE PATHWAYS OF TONGUE AND CHEEK SQUAMOUS CELL CARCINOMA

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THIS DISSERTATION IS SUBMITTED TO THE FACULTY OF DENTISTRY IN FULLFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER IN DENTAL SCIENCE

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Field of Study: Oral Oncology

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## ABSTRACT

**Introduction:**

Tongue and cheek squamous cell carcinoma (SCC) have different behaviours. In order to understand these behaviours, there is a need to look into the chromosomal alterations and gene pathways that maybe associated with oral cancer at these sites. Therefore, the objective of this study is to determine the chromosomal aberrations and gene pathways involved in tongue and cheek SCC using high resolution array based comparative genomic hybridization (aCGH).

**Methodology:**

A genome wide screening with array CGH (SurePrint G3 CGH 1x1M microarray) was performed using gDNA from 20 snap frozen fresh tissues consisting of 12 tongue and 8 cheek SCC (samples from the Malaysian Oral Cancer Database and Tumour Bank System [MOCDTBS] coordinated by OCRCC-UM). Cytosure Software was used to detect the chromosomal aberrations and candidate genes related to the selected regions. Pathway analysis was done using MetaCore$^{TM}$ software for selected genes.

**Results:**

The mean number of chromosomal aberrations per tumour for tongue SCC ($22.75 \pm 26.58$) was higher than cheek SCC ($8.63 \pm 11.89$). The most common amplified regions in tongue SCC were 8q24.22 (33.33%), 8q24.3 (33.33%), 11q13.2 (33.33%), 12q13.13 (33.33%), 14q32.33 (33.33%) and for cheek SCC the most common amplified region was 22q12.3 (25%). For the deleted regions, the most common for tongue SCC were 2q21.1 (16.67%), 6q21 (16.67%) and for cheek SCC were 2q22.1 (25%), 7q35

(25%), 19q13.33 (25%). The most significant pathway involved in tongue SCC was cell adhesion extracellular matrix (ECM) remodelling pathway, while for cheek SCC; it was cadherin-mediated cell adhesion pathway.

**Conclusion:**

This study showed that the sites of oral cancer origin have a great influence over the variations in chromosomal aberrations and gene pathways. Nevertheless, the identified chromosomal aberrations genes and their interactive pathways revealed from the present research are worth for further investigations on oral carcinogenesis. (Acknowledgment: Grant of UMRG085/09HTM and PS017/2010A)

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**List of Abbreviations**

aCGH: Array Comparative Genomic Hybridization
AJCC: American Joint Committee on Cancer
ASR: Age-Standardized rate
AURKA: Aurora kinase A
BM: Buccal Mucosa
BRCA1: Breast Cancer 1
CAMs: Cell adhesion molecules
CDKN2A: Cyclin-Dependent Kinase Inhibitor 2A
CGH: Comparative Genomic Hybridization
CHK1: Checkpoint kinase 1
CHK2: Checkpoint kinase 1
CIN: Chromosomal Instability
Cy3: Cyanine 3
Cy5: Cyanine 5
DNA: Deoxyribonucleic acid
ECM: Extracellular matrix
EGFR: Epidermal Growth Factor Receptor
EMT: Epithelial-mesenchymal transition
F: Female
FHIT: Fragile Histidine Triad
FISH: Fluorescent *in situ* hybridization
gDNA: Genomic Deoxyribonucleic acid
GLOBACAN: Global Burden of Cancer
H&E: Hematoxylin and Eosin
hTERT: human Telomerase
IACR: International Agency for Research on Cancer
ICD: International Classification of Disease
IFN: Interferon
M: Male
MAPK: Mitogen activated protein kinase
Mb: Million basepairs
MIN: Microstatellite Instability
MMPs: Matrix metalloproteinases
MNCR: Malaysian National Cancer Registry
NNK: 4-(methylnitrosoamino)-1-(3-pyridyl)-1 butanone
NNN: Nitroso-nor-nicotine
OCT: Optimal Cutting Temperature
OSCC: Oral squamous cell carcinoma
PAH: Polycyclic aromatic hydrocarbons
PDGFR: Platelet-Derived Growth Factor Receptors
PI3K- Phosphatidylinositol 3-kinase
RB1: Retinoblastoma 1
ROS: Reactive Oxygen Species
T: Tongue
TSG: Tumor suppressor gene
VEFG: Vascular Endothelial Growth Factor

**List of Symbols:**

µl: Microliter
ng: nanogram
bp: Basepairs
α: Alpha
ß: Beta