GENOTYPING FOR POLYMOPRHISM OF *STK-15*, A LOW-PENETRANCE GENE IN COLORECTAL CANCER

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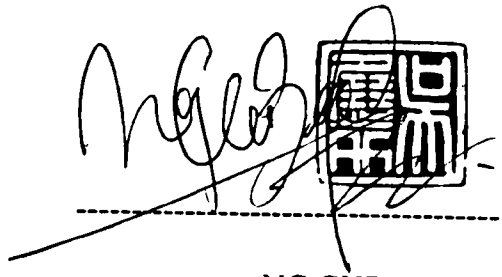

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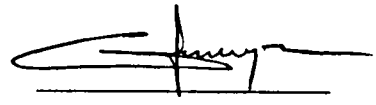

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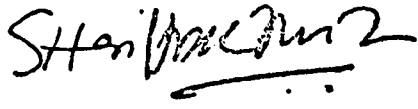

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ABSTRACT

STK-15 protein or Aurora-A kinase play a vital role in regulating the cell division process. This preliminary study was conducted to investigate the association of polymorphisms Phe31Ile with colorectal cancer development. This non-synonymous coding region was believed to have important function in regulating the periodically proteasomal-ubiquitination degrading mechanism of STK-15 protein. To examine whether functional variation in *STK-15* may affect the susceptible risk, DNA samples from colorectal cancer patients (n = 11) and healthy individual (n = 1) were genotyped for Phe31Ile polymorphisms. Polymerase chain reaction-restriction fragment length polymorphism was used in this study. A restriction enzyme cutting site of *ApoI* is created when there is a polymorphism. Out of 11 samples, 9.09% were *Phe/Phe* genotype, 72.73% were *Phe/Ile* genotype and 18.18% were *Ile/Ile* genotype. The heterozygous might possibly have the highest risk in developing colorectal cancer. The samples were in Hardy-Weinberg-proportion (χ^2 = 2.393, N=11). Risk of association between polymorphisms of Phe31Ile in both alleles and colorectal cancer were investigated using OR, allele *Ile* was found to have high susceptibility risk (OR=1.20, 95% CI = 0.1-22.0) as compared to allele *Phe*. However, acting as a preliminary study, data obtained indicated that high occurrence rate of Phe31Ile polymorphism can be found in colorectal cancer individuals and it is worth to conduct a large scale and well designed study in the future.

PENENTUAN GENOTIP POLIMOFISME GEN PENEMBUSAN RENDAH, *STK-15* DALAM KOLOREKTAL KANSER

ABSTRAK

Protein STK-15 atau Aurora-A kinase memainkan peranan yang penting dalam mengawal proses pembahagian sel. Kajian primary ini telah dijalankan untuk mengkaji hubungan antara polimofisme pada bahagian Phe31Ile dengan penghidapan penyakit kolorektal kanser. Ketidak-synonymous pada bahagian ini dipercayai mempunyai peranan yang penting dalam mengawal proses mekanisma penghapusan protein STK-15 melalui ubiquitin yang berlaku pada masa yang tertentu. Demi mangkaji samada variasi yang berfungsi dalam protein STK-15 ini akan menjejaskan kadar penghidapan penyakit kolorektal kanser, sampel DNA daripada penghidap penyakit kolorektal kanser (n = 11) dan seorang individu yang sihat (n = 1) telah menjalani kajian penentuan genotip polimofisme pada bahagian Phe31Ile. Kaedah tindak balas rantai polimerase-pembatasan kepanjangan jujukan DNA polimofisme telah digunakan dalam kajian ini, pemotongan pada bahagian yang tertentu oleh *ApoI* akan berlaku apabila mempunyai polimofisme. Daripada sebelas sampel yang dikumpul, 9.09% adalah *Phe/Phe* genotip, 72.73% adalah *Phe/Ile* genotip dan 18.18% adalah *Ile/Ile* genotip. Genotip heterozigot dipercayai mungkin mempunyai kadar risiko penghidapan penyakit kolorektal kanser yang paling tinggi. Kesemua sampel berada dalam keseimbangan Hardy-Weinberg (χ^2 = 2.393, N=11). Hubungan antara kadar risiko penghidapan penyakit kolorektal kanser dan Phe31Ile polimofisme dalam kedua-dua alle telah dikaji menggunakan kaedah nisbah keganjilan (OR), alle *Ile* didapati mempunyai kadar risiko yang tertinggi dalam sehubung dengan penyakit kolorektal kanser ini (OR = 1.20, 95% CI = 0.1-22.0) berbanding dengan alle *Phe*. Walaubagaimanapun, sebagai kajian primary, data daripada kajian ini jelas menunjukkan bahawa terdapat kadar polimofisme Phe31Ile yang tinggi dalam pesakit kolorektal kanser, ini menunjukkan bahawa adalah berbaloi untuk menjalankan kajian ini dengan saiz sampel yang besar pada masa akan datang.

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LIST OF SYMBOLS, UNITS AND ABBREVIATION

w/v	weight over volume
v/v	volume over volume
%	percent
s	second
ml	mililiter
µl	microliter
°C	degree Celcius
r.p.m	rotation per minute
M	Molar
mM	miliMolar
µM	microMolar
mm	millimeter
mg/ml	milligram per milliliter
min	minute
V	volt
DNA	deoxyribonucleic acid
PBS	phosphate-buffer-saline
RT	room temperature
TE	Tris-EDTA
PCR	polymerase chain reaction
dNTP	deoxynucleotides-triphosphate
NaOH	sodium hydroxide
HCl	hydrochloride
BSA	bovine serum albumin
UV	ultraviolet
dH_2O	distilled water
BTAK	Breast Tumour Amplified Kinase
STK-15	serine/threonine kinases-15
SNP	single nucleotide polymorphism
MSI	microsatellite instability

MMR	mismatch repair
CRC	colorectal cancer
GST	glutathione *S*-Transferase
GSTO	gluhthione *S*-Transferasc Omega
XRCC3	X-ray cross complementing-3
Thr	threonine
Met	methionine
PAI-1	plasminogen activator inhibitor-1
MTHFR	methylenetetrahydrofolate reductase
NAT-2	*N*-acetyltransferase-2
VDR	vitamin D receptor
COX-2	cyclooxygenase-2
TS	thymidylate synthase
dTMP	deoxythymidine monophosphate
dUMP	deoxyuidine monophosphate
5-FU	5-fluorouracil
PP1	protein phosphate 1
Cdk	cyclin-dependent kinase
CIP	Cdks inhibitory protein
INCENP	inner centromere protein
ALDH	alcohol dehydrogenase
CYP	Cytochrome P450
XME	xenobiotic metabolizing enzymes
XPD	xeroterma pigmentosum group D
WRN	Werner syndrome gene
UGT	UDP-glucuronosyltransferase
ADR	adverse drug effect
FGD	familial glucocorticoid deficiency
MRAP	melanocortin 2 receptor accessory protein
OA	osteoarthritis
AKR1B1	aldose reductase
SULTIA1	sulfotransferase A1
G	glycine

Q	glutamine
D	aspartic acid
R	arginine
Y	tyrosine
A	alanine
K	lysine
T	threonine
C	cysteine
S	serine
F	phenylalanine
I	isoleucine
FAP	Familial Adenomatous Polyposis
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
OR	Odds ratio
CI	Confidence interval
df	Degrees of freedom

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CHAPTER 1

INTRODUCTION

1.1 Introduction

STK-15, which is also known as Aurora-A, Aurora-2 or Breast Tumour Amplified Kinase (abbreviated as BTAK for its first discoveries in breast tumour), can be clarified also as STK-6 for its homologues found in *Drosophila melanogaster* or AIR-1 in *C. elegans*. STK-15 belongs to one of the family of mitotic kinases, which is a type of serine/threonine kinases, primary known as Aurora kinases/Ipl1-related kinases. (Dai *et al.*, 2004; Marumoto *et al.*, 2005). Research and studies have been conducted to show that the Aurora kinases play vital role in regulating the progression of cell cycle especially in controlling some of the major events like centrosome maturation, chromosome condensation, centrosome separation, degradation of nuclear-envelope, the congregation of bipolar-spindle, chromosome segregation and the process of cytokinesis (Zhou *et al.*, 1998; Gritsko *et al.*, 2003; Li *et al.*, 2003; Marumoto *et al.*, 2005).

Studies have shown that human comprises three classes of Aurora kinases—Aurora-A, Aurora-B and Aurora C. Research had also indicated that all the three classes of Aurora kinases are involved in the development of different types of cancer. However, in this research, only the class STK-15/Aurora-A will be further elucidated. STK-15/Aurora-A is being found to express mostly in all the types of cells and specifically, the protein STK-15/Aurora-A is being coded by the gene STK-15 is found to be located on the chromosome 20q13.2.

As for this dissertation, we are going to examine the effect of the mechanism of polymorphisms on this putative oncogene STK-15/Aurora-A specifically for colorectal cancer patients. Research has shown that STK-15/Aurora-A is being overexpressed and amplified during the progression of cell-cycle and leads to the development of cancer. Many types of cancer are involved such as breast cancer, colorectal cancer, pancreatic cancer (Li *et al.*, 2003), prostate cancer, ovarian cancer, neuroblastoma cancer, cervical cancer, lung cancer, renal cancer, gastric cancer and melanoma cell lines. (Bischoff *et al.*, 1998; Zhou *et al.*, 1998).

However, polymorphisms of STK15/Aurora-A is not the sole cause that leads to the onset of colorectal cancer since it also possesses three other major reasons such as the mutations in tumour suppressor genes, oncogenes and DNA mismatch repair genes. Since both polymorphisms and the presence of low penetrance genes have been the useful biomarkers for the signal of cancer development, therefore, both searching for polymorphisms and low penetrance genes have been utilized as one of the effective methodology in knowing the potential of a patient to develop cancer at the present days.

Despite there have been numerous volumes of literatures regarding the colorectal cancer at the present days, patients developing this type of cancer had never been reduced. In year 2006, there were more than 55,000 cases of death solely belongs to colorectal patients in United States (Hung *et al.*, 2006) and as for Malaysia, colorectal cancer had become the leading type of diseases. This entire phenomenon conveys a message for us that there is still a compelling need to search for new therapies and detection methods for this cancer.

1.2 Objectives

The Main Objectives of this dissertation are:

(i) To extract DNA from biopsy samples of colorectal cancer.

(ii) To test the presence of Phe31Ile single nucleotide polymorphism (SNP) in putative oncogene *STK15*/Aurora-A.

(iii) To investigate to what extent the single nucleotide polymorphism of Phe31Ile in STK-15 associated with susceptibility risk in developing colorectal cancer.

CHAPTER 2

LITERATURE REVIEW

2.1 What is Colorectal Cancer?

Colon Cancer or more accurately being known as colorectal cancer is being defined as clusters of malignant (cancerous) cells form and develop surrounding the tissues of the colon organ within our stomach (Feldman *et al.*, 2002; Warrell *et al.*, 2003).

2.1.1 The Biology of Normal Colon

As in a normal condition of the organ colon, it comprises a single layer of column-like shape of epithelial cells which are being organized into invaginations, primary known as crypts. When we observed carefully, we will be able to discover that those crypts can actually being subdivided into two distinct zones. The first zone belongs to a proliferative compartment, which comprises cells at the bottom portion of the crypts. While for the second zone, it comprises cells in the upper portion of the crypts and this zone is known as differentiated zone (Warrell *et al.*, 2003).

2.1.2 The Biology of Colorectal Cancer

Colorectal cancer can only be onset when a structure known as polyps started to develop. This polyps structure basically can be defined as a growth arising from the intestine itself, protruding into the lumen of the colon. Sometimes also being known as lesions and these polyps can be seen through naked eyes (visible).

This polyps basically can be arisen from different parts of the colon, sometimes it might arise from subepithelial tissues and sometimes it might arise from the intestinal epithelium. Polyps arising from the latter can be the matter of life and death since it can be the precursor for the development of colorectal adenocarcinomas. When we come across the disease cancer, we can classify its severity based on its histology. As for the disease of cancer, term "benign" is used for no life-threatening condition and the term "malignant" for harmful or likely to cause death.

Polyps have the same situation at where whether it is benign or malignant, it thoroughly based on its histology. As for colorectal cancer, we have the term "non-neoplastic" for benign or very unlikely to transform into malignancies and "neoplastic" for malignant or very likely to develop malignancies (Kim and Lance, 1997). Under the histology studies, colorectal cancer will be declared officially when a neoplastic stage has achieved. However, a recent study on hyperplastic polyps, which is the enlargement or unusual growth within the colon, which is normally cause by an abnormal increased of cells do shown an increased risk in developing colorectal cancer (Rashid *et al.*, 2000).

As for neoplastic in colorectal cancer is known as adenomatous polyps. Patients who develop these polyps are very likely or have higher percentage to develop malignancies. They can be further classifies into low-, medium- and high-grade. As in high-grade stage, the polyps normally can reach the size of about 1 cm and are villous (hairy) (Appel *et al.*, 1977). Study has also shown that in order to develop colorectal cancer from small polyps, normally it has to take eleven years to bring it on (Stryker *et al.*, 1987).

Studies have also proven that the locations of those polyps are also affecting the development of colorectal cancer. According to the studies, polyps locating at the left side of the colon will be more susceptible to develop colorectal cancer (Vatn M. H and Stalsberg H., 1982; Williams *et al.*, 1982; Coode *et al.*, 1985; Johannsen *et al.*, 1989).

2.2 The Genetics of Colorectal Cancer

One of the causes for colorectal cancer (CRC), in fact we should say that this is the major cause contributing to the development of CRC, will be the mutations of certain genes. CRC arise from mutations in multiple cancer causing-genes in colonic epithelial cells, at where it had been mentioned by Balmain and his colleagues that most cancer is a polygenic disorder (Balmain *et al.*, 2003).

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