

# Identification of KRAS gene codon 12 polymorphism in colorectal cancer patients at Mohammad Hoesin General Hospital Palembang

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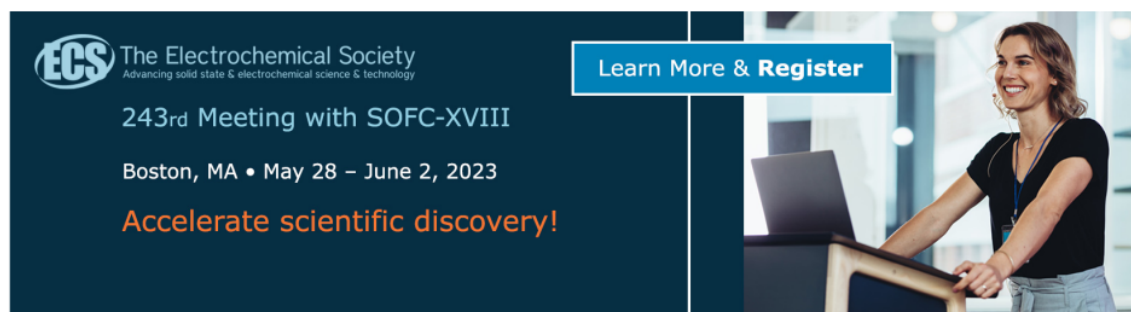
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## Identification of KRAS gene codon 12 polymorphism in colorectal cancer patients at Mohammad Hoesin General Hospital Palembang

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**Abstract.** Colorectal cancer occurs due to neoplastic transformation of epithelial cells in the colon and rectum resulting from the accumulation of *genetic* and *epigenetic* aberrations. One of the genetic factors associated with colorectal cancer is KRAS gene polymorphism, which mostly occurs in codon 12. KRAS gene polymorphism leads to constitutional activation of KRAS protein effectors which will initiate signalling network to nucleus to increase cell proliferation, survival and differentiation. The aim of this study was to identify the KRAS gene codon 12 polymorphism in colorectal cancer patients at Mohammad Hoesin General Hospital Palembang. This study was a descriptive laboratory study with PCR-RFLP technique using BstNI enzyme on thirty patients with colorectal cancer. Wild type genotype (GG) of KRAS gene codon 12 found in 15 patients (50%), heterozygous mutant genotype (Gg) found in 12 patients (40%) and homozygous mutant genotype (gg) only found in 3 patients (10%). The G allele frequency was 70% and the g was 30%. The most common genotype found in colorectal cancer patients was GG genotype and most common allele was G allele. KRAS gene polymorphism was found in half of the colorectal cancer patients, heterozygous mutant genotype (Gg) was more frequent than homozygous mutant genotype (gg).

### 1. Introduction

Colorectal cancer (CRC) is a disease arising from neoplastic transformation of epithelial cells in the colon and rectum as a result of accumulations of genetic and epigenetic aberrations and environmental factors [1]. CRC is the third most common cancer and is the third-highest cause of mortality in the United States. In 2011, 141,210 people were diagnosed with CRC and 49,380 deaths were attributed to CRC [2]. Data from the Indonesian Department of Health stated 28.17% of all cancers in Indonesia had been CRC. In 2002, there were over 1 million cases of CRC with a mortality rate of over 50%. CRC affected 9.5% of male cancer patients and 9.3% of female cancer patients [3]. Risk factors associated with CRC include obesity, high fat and alcohol intake, red meat consumption, inadequate daily physical activity, smoking, and genetic factors, namely family members with CRC and inflammatory bowel disease (IBD) [2].



The genetic basis of the development of CRC involves mutations [3]. One of the genetic predispositions known to play a role in CRC is the KRAS gene. The KRAS gene codes the KRAS protein, a G-protein located in the cell membrane and is involved in signal transductions [4]. The KRAS gene is a proto-oncogene, hence mutations in one allele would cause disturbances in the cell cycle [5]. Polymorphisms in the KRAS gene causes loss of the KRAS' protein's ability to hydrolyze GTP, causing KRAS to constantly be in active state and leading to constitutional activation of various effector pathways signaling the nucleus to increase proliferation, integrity, and differentiation of the cells [6].

Approximately 30-60% of CRC patients around the world and 16.3% of Indonesian CRC patients had polymorphisms in the KRAS gene [7,8]. The most common locations of the KRAS gene polymorphisms are codons 12 (28%) and 13 (8%) in exon 1, and rarely in codon 61 [9]. In Indonesia, Maliza et al. reported 20% patients had the codon 12 polymorphism, and the codon 13 polymorphism was not identified [10]. Polymorphisms in the KRAS gene is often identified in CRC with more aggressive phenotype and resistance towards epidermal growth factor receptor (EGFR) monoclonal antibody therapy, such as cetuximab or panitumumab [12]. Early identification of KRAS gene polymorphisms in CRC patients may help in determining the best therapeutic option [10,11]. So far, there had been limited data on the distribution of KRAS gene codon 12 polymorphism in CRC patients, especially in Palembang.

## 2. Methods

A laboratory-based descriptive study was conducted using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP).

CRC patients seeking treatment at Digestive Surgery Department of Dr. Mohammad Hoesin General Hospital were recruited into this study, excluding patients with coexisting other malignancies. The diagnosis of CRC was confirmed with histopathological examination. Thirty subjects were recruited during May through July 2014.

DNA was isolated from blood samples through Chelex-100 method. Isolates were then amplified using polymerase chain reaction in 25  $\mu$ l mixtures containing 10  $\mu$ l *GoTaq Green* mix of dNTP and *Taq* polymerase (Promega, USA), 9  $\mu$ l ddH<sub>2</sub>O, a pair of primers, and 5  $\mu$ l template DNA. The primer pair sequences used were 5'-ACT GAA TAT AAA CTT GTG GTA GTT GGA CCT-3' (forward) and 5'-TAA TAT GTC GAC AAA CAA GAT TTA CCT C -3' (reverse) [12]. Amplification was carried out using *i-cycler* (Biorad).

Amplified DNA fragment was then digested with *Bst*NI endonuclease restriction enzyme at 60°C. Obtained digestion product was loaded into 2% agarose gel stained with 0.1% ethidium bromide for electrophoresis and visualized under UV transillumination.

Two bands were generated for the wild type KRAS genotype (106bp and 26bp). Presence of the codon 12 mutation causes the loss of restriction site for *Bst*NI in the amplified sequence, generating one 135bp band [12].

## 3. Results

The mean age of the study's subjects was  $51,6 \pm 13,14$  years (age range: 31-87 years), mostly within the  $\geq 50$  years old age group, with more females than males. The rectum was more common as tumor location than colon (table 1).

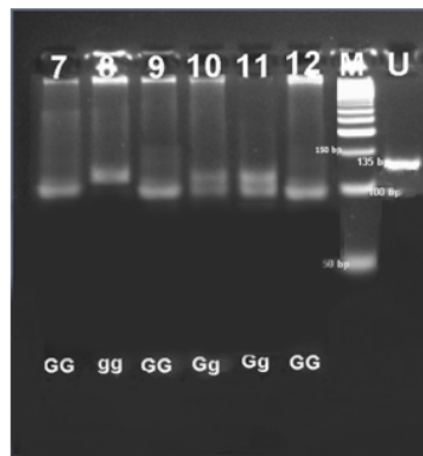
In the visualized electrophoresis product, the 26bp band was not visible, hence the genotypes were visualized as follows: one 106bp band was generated for the wild type (GG) genotype, two bands (135bp and 106bp) for the heterozygous mutant (Gg) genotype, and one 135bp band for the homozygous mutant (gg) genotype (figure 1).

Twelve subjects (40%) had heterozygous mutant (Gg) genotype, and three subjects (10%) had homozygous mutant (gg) genotype. The frequency for the polymorphic allele *g* was 30% ( $n = 18$ ) (table 2).

The KRAS codon 12 polymorphism was most commonly identified in the 40-49 years old age group (23,3%), more common among females (26,7%) than males (23,3%), and mostly identified in patients with colonic tumors (26,7%) compared to those with rectal tumors (23%) (table 3).

**Table 1.** Subject characteristics.

Subject Characteristic	n= 30	(%)
Age (years)		
< 40	5	16,7
41-49	11	36,7
≥ 50	14	46,6
Sex		
Male	14	46,7
Female	16	53,3
Tumor Location		
Colon	11	36,7
Male	5	16,7
Female	6	20
Rectum	19	63,3
Male	9	30
Female	10	33,3



**Figure 1.** Visualized RFLP product. M: 50bp ladder marker; U: uncut (undigested amplicon); 7-12: sample order. Samples 7,9, and 12 had wild type (GG) genotype, samples 10 and 11 had heterozygous mutant (Gg) genotype, and sample 8 had homozygous mutant (gg) genotype.

#### 4. Discussions

In this study, most patients with CRC are in the  $\geq 50$  years age group (46.6%). This finding further supports previous results from Soefyani et al at Jakarta [13], where 46.5% of CRC patients were  $\geq 50$  years of age. Age is a risk factor to the occurrence of CRC. CRC incidence increases past the age of 40 and reaches its peak over the age of 50. More than 90% of CRC cases were diagnosed at over 50 years of age [14]. In spite of this, CRC may occur at any age [15]. According to Sudoyo et al [16], CRC in Indonesia is mostly found in working age group. CRC incidence is related to both genetic and environmental factors, such as diet, alcohol consumption, smoking, etc [17].

The incidence of CRC in this study was found to be higher in females (53.33%). This finding is in accordance with Imamura et al's findings where females more frequently had CRC (55%) [18]. Yet, this contradicts results obtained by Li et al [7] in China, in which CRC was more commonly found in males (55.1%). Cora et al [19] stated that there are other factors that may act as risk factors in the

development of CRC, such as alcohol consumption, smoking, and high-fat, low-fibre diet. These risk factors affect males and females equally in the carcinogenesis of CRC.

**Table 2.** KRAS codon 12 polymorphism genotype and allotype distribution.

Characteristic	<i>N</i>	%
<i>Genotype</i>		
Wild type (GG)	15	50
Heterozygous mutant (Gg)	12	40
Homozygous mutant (gg)	3	10
<i>Allotype</i>		
Wild type (G)	42	70
Polymorphic (g)	18	30

**Table 3.** KRAS codon 12 polymorphism distribution based on subject characteristics.

Characteristic	KRAS codon 12			
	Wild type		Polymorphic	
	n	%	n	%
<i>Age (years)</i>				
<40	3	10	2	6,7
40-49	4	13,3	7	23,3
≥ 50	8	26,7	6	20
<i>Sex</i>				
Male	7	23,3	7	23,3
Female	8	26,7	8	26,7
<i>Tumor Location</i>				
Colon	3	10	8	26,7
Rectum	12	40	7	23,3

The frequency of tumors in the rectum was found to be higher (63.3%) than in colon, similar to the findings of Li et al [7] where 51.2% of tumors occurred in the rectum. Rectal cancer occurred more frequently in this study's female subjects (33.33%). This is similar to the study by Baskin et al [17] on Turkish population, in which rectal cancer had been more common in females (51.4%). The factors affecting this difference in location of tumors are related to feeding pattern, which in turn affects transit time in the colon and bacterial fermentation of carbohydrate, free fatty acid synthesis, and the exposure of carcinogenic food ingredients to the colonic and rectal epithelia. The high prevalence of rectal tumors might be related to the fecal concentration and longer transit time in the rectum, which frequently cause constipation [20]. Zhao et al [21] stated that transit time in the colon and constipation frequency are higher in females than males.

In this study's subjects, the genotype frequency of polymorphic type KRAS codon 12 was 50%, higher than that of RASCAL I (21%) [22] and RASCAL II (26%) [23], also in studies conducted at the United States (22.7%) [24], Romania (46.7%) [12], Japan (31%) [25], China (33.3%) [7], Spain (48%) [26], Iraq (48%) [27], and Jakarta (16.3%) [8], but lower than findings in Italian (52.5%) [28] and Makassarese (58,1%) populations [29].

The frequency of polymorphic KRAS codon 12 genotype is highest in the 40-49 years age group (23.33%). This further supports previous findings by Shahana (2012) in the Indian population that showed highest frequency of polymorphic KRAS codon 12 genotype in the >40 years age group (29%) [30].

Gender-wise, the frequency of the polymorphic KRAS codon 12 genotype was found to be higher in females (26.67%), similar to Shen et al's [31] findings in China and Watanabe et al's [32] study in



Japan, where mutations in the KRAS gene had also occurred more frequently in females (44.7% and 40.9%, respectively), yet differs from the Australian study by Rosty et al [33] which showed the KRAS codon 12 polymorphism being more common in males (58%).

The polymorphic KRAS codon 12 genotype was more frequent in patients with colonic tumor (26.67%). Similarly, Abboud et al [34] in the United States found that this polymorphism occurs more frequently in colonic tumor patients (46%). But, a Turkish study by Baskin et al [17] found that this polymorphism is more common in rectal tumor patients (34.3%). The KRAS gene polymorphism is identified in about 30-60% of CRC patients worldwide [7], and over 90% was identified in codon 12 [35]. Mutations in codon 12 localizes near the GTP binding site and disrupts the hydrolysis of GTP, which is important to convert the KRAS protein to inactive form. This causes the KRAS protein to constantly be in active form, signalling the nucleus to increase cell proliferation, defense, and differentiation, which eventually leads to malignancy.

Several factors affect the distribution of the KRAS codon 12 polymorphism, namely geographic, environmental, lifestyle, and ethnic factors, which may influence epigenetic regulation of the KRAS oncogen. Low-folate, high-fat diet, smoking, and alcohol consumption may also be related to KRAS oncogen activation in the carcinogenesis of CRC [17].

## 5. Conclusions

In this study, the most commonly identified genotype was GG and the most common allele was G. In 30 CRC patients, 15 patients (50%) were polymorphic for KRAS codon 12, where 12 of them (40%) had heterozygous mutant genotype (Gg) and 3 (10%) had homozygous mutant genotype.

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