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Susceptibility and severity of cancer-related fatigue in colorectal cancer patients is associated with *SLC6A4* gene single nucleotide polymorphism rs25531 A > G genotype

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ABSTRACT

Purpose: To explore the correlation between the SERT gene promoter single nucleotide polymorphisms (SNPs) rs25531 and rs956304 and the cancer-related fatigue (CRF) of colon and rectal cancer, and also to analyze the correlation of the interaction of genetic and non-genetic factors.

Method: A sample of 568 colon and rectal cancer patients were recruited from the Second Affiliated Hospital of Nanchang University from October 2013 to December 2015. The Chinese version of the Brief Fatigue Inventory (BFI-C) was used to evaluate the CRF. The genomic DNA was extracted from peripheral blood samples of the patients. Direct sequencing was used to determine the rs25531 and rs956304 genotypes.

Results: Compared with the AA genotype, the risk of suffering from CRF and the severity of CRF increased to 1.77 times (95% CI = 1.22–2.59, P = 0.003) for patients who carry with G allele (AG + GG genotype) at rs25531 locus.

Conclusions: The SERT gene promoter SNP rs25531 was associated with the CRF in patients with colon and rectal cancer and the G genotype was an independent risk factor for CRF among individuals with colon and rectal cancer in the study.

1. Introduction

Colon and rectal cancer is the third most commonly diagnosed cancer in males and the second in females worldwide, with an estimated 1.4 million cases and 693,900 deaths occurring every year (Torre et al., 2015). In contrast to incidence trends, decreasing colon and rectal cancer mortality rates have been observed in a large number of countries worldwide (Edwards et al., 2010). With the transformation to patient-centered medical care model, we should focus on palliation of symptoms in addition to prevention, early detection, and management of cancer. In other words, caregiving goals should include the improvement of patient's quality of life.

Fatigue is the most prevalent cancer-related symptom and has a significant adverse impact on patients' functional ability and quality of life (Bennett et al., 2016; Bower, 2014). Cancer-related fatigue (CRF) has been defined as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning (Berger et al., 2015). Patients perceive fatigue to be the most distressing symptom associated with cancer and its treatment, more distressing even than pain or nausea and vomiting (Spathis et al., 2015; Wang and Woodruff, 2015). It is estimated that approximately 60–96% of cancer patients experience fatigue (Berger et al., 2012; Noal et al., 2011; Seruga et al., 2008). And low level of fatigue independently predicted longer recurrence-free and overall survival in primary breast cancer patients (Groenvold et al., 2007). Therefore, CRF is worthy of more attention from researchers and clinicians.

The specific mechanisms involved in the pathophysiology of CRF are unknown. Proposed mechanisms include hypothalamic-pituitary-adrenal (HPA) axis dysregulation, circadian rhythm desynchronization, pro-inflammatory cytokines, skeletal muscle wasting, and genetic dysregulation (Bower, 2014; Bower and Lamkin, 2013; Pachman et al., 2012). There is increasing evidence for a role for serotonin receptors, also known as 5-hydroxyrtyptamine receptors (5-HT) in the genesis of central fatigue (Bozina et al., 2012; Meyer et al., 2015; Ryan et al., 2007). The level of 5-HT in the synaptic cleft is mainly regulated by the 5-HT transporter (5-HTT). The serotonin transporter (SERT or 5-HTT) is a protein that encoded by the *SLC6A4* gene. The gene was mapped to human chromosome 17q11.1–17q12. The SERT is a type of monoamine

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Table 1
Basic definitions of genetic terms.

Terms	Basic definition
Minor allele frequency (MAF)	MAF refers to the frequency at which the second most common allele occurs in a given population. In other words, if there are 3 alleles, with frequencies of 0.50, 0.49, and 0.01, the MAF will be reported as 0.49.
Allele	Humans have two sets of chromosomes, which are referred to as homologous chromosomes. The "allele" represents a gene that can occupy the same position on homologous chromosomes and that control the same character.
Up-regulate	The complementary process that involves increases of such components is called up-regulation.
A > G	Wild type refers to the phenotype of the typical form of a species as it occurs in nature. Originally, the wild type was conceptualized as a product of the standard "normal" allele at a locus, in contrast to that produced by a non-standard, "mutant" allele. In the polymorphic locus rs25531, "A" represents wild-type, and "G" represents a mutant-type. A > G represents A genotype mutation to G genotype.
(GG + AG) versus AA	If both alleles at a gene on the homologous chromosomes are the same, they and the organism are homozygous with respect to that gene. If the alleles are different, they and the organism are heterozygous with respect to that gene. AA represents wild-type homozygous, AG represents heterozygote, and GG represents mutant homozygote. (GG + AG) versus AA indicates that the phenotype of the G allele is compared to the phenotype of the A allele

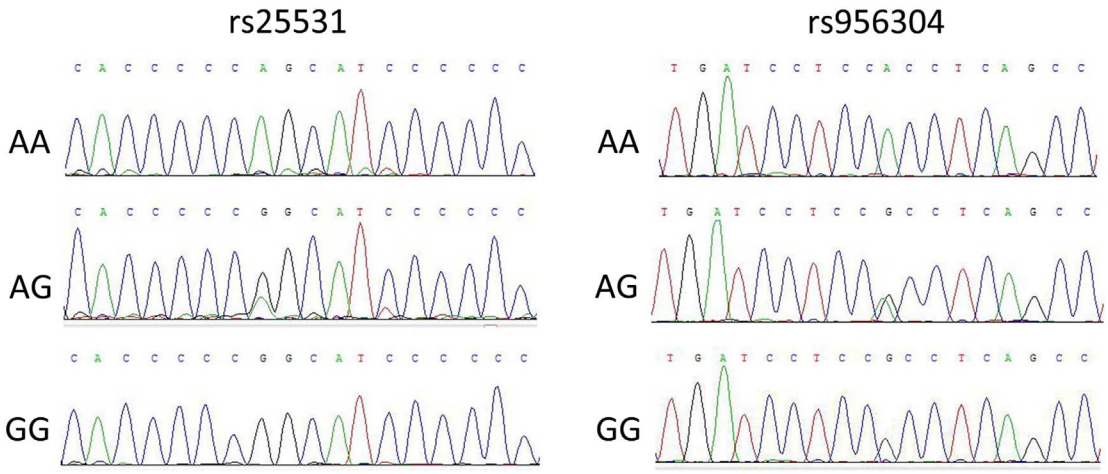

Fig. 1. Sequencing results of SNP rs25531 and rs956304 genotypes.

Table 2
Single Factor Analysis of CRF in patients with colorectal cancer.

		No, n (%)	Mild, n (%)	Moderate, n (%)	Severe, n (%)	χ^2 values	P values
Age (Year)	≤60	52 (17.1)	100 (32.9)	112 (36.8)	40 (13.2)	4.188	0.042
	> 60	24 (9.1)	100 (37.9)	88 (33.3)	52 (19.7)		
Gender	Male	44 (14.1)	152 (48.7)	76 (24.4)	40 (12.8)	33.54	< 0.001
	Female	32 (12.5)	48 (18.8)	124 (48.4)	52 (20.3)	0	
Physical exercise state	Yes	44 (21.3)	91 (44.0)	48 (23.2)	24 (11.6)	34.49	< 0.001
	No	32 (8.9)	109 (30.2)	152 (42.1)	68 (18.8)	9	
BMI (kg/m^2)	≤23.9	45 (13.6)	117 (35.2)	121 (36.4)	49 (14.8)	2.136	0.344
	24.0–27.9	21 (11.2)	67 (35.6)	64 (34.0)	36 (19.1)		
	≥28.0	10 (20.8)	16 (33.3)	15 (31.3)	7 (14.6)		
Smoking	Yes	28 (10.9)	68 (26.6)	96 (37.5)	64 (25.0)	28.17	< 0.001
	No	48 (15.4)	132 (42.3)	104 (33.3)	28 (9.0)	1	
Drinking	Yes	12 (9.8)	44 (35.8)	43 (35.0)	24 (19.5)	1.640	0.200
	No	64 (13.4)	156 (35.1)	157 (35.3)	68 (15.3)		
Tumor type	Colon cancer	32 (11.0)	112 (38.4)	108 (37.0)	40 (13.7)	0.076	0.783
	Rectal cancer	44 (15.9)	88 (31.9)	92 (33.3)	52 (18.8)		
Tumor stage (TNM)	StageI	28 (31.8)	40 (45.5)	16 (18.2)	4 (4.5)	60.61	< 0.001
	StageII	20 (10.9)	72 (39.1)	72 (39.1)	20 (10.9)	3	
	StageIII	28 (10.3)	84 (30.9)	104 (38.2)	56 (20.6)		
	StageIV	0 (0.0)	4 (16.9)	8 (33.3)	12 (50.0)		
Chemotherapy	Yes	12 (5.6)	56 (25.9)	92 (42.6)	56 (25.9)	50.09	< 0.001
	No	64 (18.2)	144 (40.9)	108 (30.7)	36 (10.2)	6	
Radiotherapy	Yes	8 (13.6)	16 (27.1)	22 (37.3)	13 (22.0)	1.567	0.211
	No	68 (13.4)	184 (36.1)	178 (35.0)	79 (15.5)		
rs25531	AA	64 (14.7)	170 (39.0)	140 (32.1)	62 (14.2)	27.63	< 0.001
	AG	10 (8.3)	29 (24.0)	56 (46.3)	26 (21.5)	6	
	GG	2 (18.2)	1 (9.1)	4 (36.4)	4 (36.4)		
	AG + GG	12 (9.1)	30 (22.7)	60 (45.5)	30 (22.7)		
rs956304	AA	65 (13.3)	166 (33.9)	173 (35.4)	85 (17.4)	2.991	0.084
	AG	10 (13.5)	31 (41.9)	26 (35.1)	7 (9.5)		
	GG	1 (20.0)	3 (60.0)	1 (20.0)	0 (0.0)		
	AG + GG	11 (13.9)	34 (43.0)	27 (34.2)	7 (8.9)		