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Polymorphisms in the MDM2 promoter and risk of breast cancer: a case-control analysis in a Chinese population ☆

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Abstract

MDM2 is a phosphoprotein that interacts with P53 and inhibits its activity. Recently, a T/G substitution (SNP309) in the promoter of *MDM2* was identified and has been demonstrated to be associated with an increased MDM2 expression and a significantly earlier age of onset of several tumors, including breast cancer. To test the hypothesis that this functional variant in the *MDM2* promoter is associated with risk of breast cancer, we conducted a molecular epidemiological study of 366 breast cancer cases (BC), 263 patients with benign breast diseases (BBD) and 605 cancer-free controls in China, in which we genotyped this T/G variant and another common insertion/deletion polymorphism (Del1518) in the *MDM2* promoter and evaluated the associations between these two polymorphisms and breast cancer risk. We found that the variant allele frequencies of these two polymorphisms were not statistically different between the cases and controls (SNP309G: 0.500, 0.542, and 0.506 in BC, BBD, and controls, respectively, and Del1518−: 0.296, 0.308, and 0.297 in BC, BBD, and controls, respectively). Logistic regression analyses revealed that the variant genotypes of both *MDM2* SNP309 and Del1518 polymorphisms were not significantly associated with risk of breast cancer (adjusted OR, 1.03; 95% CI, 0.74–1.42 for SNP309 *TG* and GG; and adjusted OR, 1.09; 95% CI, 0.83–1.43 for Del1518 +/− and −/−). These findings suggest that these two *MDM2* promoter variants may not play a major role in the etiology of breast cancer.

Keywords: MDM2; Genetic polymorphism; Breast cancer; Molecular epidemiology

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1. Introduction

Breast cancer is the most common cancer among women worldwide, and more than 1,000,000 new cases are diagnosed every year [1]. In China, the incidence rate of breast cancer has been significantly increasing both in urban and rural areas in last three decades [2]. Although the researchers have reached a consensus that breast cancer is resulted from multiple environmental factors as well as genetic alterations, such as genetic polymorphisms [3,4], the exact molecular mechanisms of breast cancer are still under intensive investigation.

Among the genetic alterations, the tumor suppressor protein, P53, is a principal mediator of multiple cellular functions, including growth arrest, senescence, and apoptosis in response to cellular damage [5,6]. The activity of P53 may either be inactivated or be attenuated in a vast majority of human cancers through mutations in the *P53* gene or aberrant expression of proteins acting in the P53 pathway, such as MDM2 [7].

MDM2 coded by the Murine Double Minute2 (*MDM2*) gene, is an important negative regulator of P53. Besides its directly inhibiting the transcriptional activity of P53, MDM2 also stimulates the nuclear export and proteolytic degradation toward P53 as an E3 ubiquitin ligase [8–10]. Overexpression of MDM2 is observed both in epithelial cells of transgenic mice with induced mammary carcinomas [11] and in multiple human tumors, including breast cancer [12–15]. Jones et al. reported that massive overexpression of a full-length *MDM2* cDNA in the mammary epithelium of transgenic mice inhibited normal development of the mammary gland and increased papilloma formation [16]. Furthermore, amplification of the *MDM2* gene is more frequent in cancer cells with the wild-type P53 than in cells with the mutant or deleted P53, which might suggest that overexpression of MDM2 can substitute for inactivated P53 by mutation [17–20].

The human *MDM2* gene comprises two promoters, a constitutive promoter and a P53-response intronic promoter [21]. Recently, a novel T to G substitution located in the intronic P53-response promoter of *MDM2*, named SNP309, has been identified, which was found to increase the affinity of the transcriptional activator Sp1 and subsequently resulted in higher expression levels of *MDM2* RNA and protein [22]. Moreover, a clinical epidemiological study showed that individuals carrying the G allele of SNP309 had a significantly earlier age of onset of both hereditary and sporadic cancers [22]. Specifically, hereditary Li–Fraumeni individuals carrying the G allele of SNP309 developed breast cancer on average 10 years earlier than those who did not [22]. Therefore, it is hypothesized that this functional variant in the *MDM2* promoter may contribute to individual's susceptibility to breast cancer. In addition, in the SNP databases, we also searched for genetic variants in the *MDM2* constitutive promoter and found a common 40-bp insertion/deletion polymorphism (Del1518) at −1518 position (http://egp.gs.washington.edu/), which contains a putative TATA motif.

To test the hypothesis that the functional variants in the *MDM2* promoter are associated with risk of breast cancer, we conducted a molecular epidemiological study of breast cancer in a Chinese population, genotyped both SNP309 and Del1518 polymorphisms in 366 breast cancer cases, 263 BBD and 605 cancer-free controls, and evaluated the association between these two polymorphisms and breast cancer risk.

2. Materials and methods

2.1. Study subjects

This hospital-based case–control study included 629 cases with breast diseases (366 breast cancer cases, 263 patients with BBD) and 605 cancer-free controls. All subjects were genetically unrelated ethnic Han Chinese women from Nanjing City and surrounding regions in southeast China. Patients with mammary lump who underwent surgical treatment were consecutively recruited from the Cancer Hospital of Jiangsu Province, the First Affiliated Hospital of Nanjing Medical University and the Gulou Hospital, Nanjing, China between January 2004 and February 2005. After histopathological diagnosis, the above patients were categorized as breast adenocarcinoma (356 invasive, 10 in situ) and BBD. Cancer-free controls were randomly selected from a pool of 10,500 individuals participated in a community-based screening program for non-infectious diseases conducted in Jiangsu province during the same time period as the cases were recruited, and were frequency-matched to the cases on age (±5 years). After informed consent was obtained, each subject was personally interviewed by trained interviewers using a pre-tested questionnaire to obtain information on demographic data, menstrual and reproductive history, lifestyles, and environmental exposure history. After interview, an approximately 5-ml venous blood sample was collected from each subject. The study was approved by the institutional review board of Nanjing Medical University.