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Zinc transporter *SLC39A11* polymorphisms are associated with chronic gastritis in the Korean population: the possible effect on spicy food intake

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ABSTRACT

Herein, we hypothesized that *ZIP11* variants would be important risk factors for chronic gastritis and that there would be an interaction effect of the relationship between their variants and spicy food intake on the development of chronic gastritis. Participants in this cross-sectional study (n = 3882 + 252) were recruited from a cohort of the Korean Genome and Epidemiology Study in 2001. Age, sex, education, smoking and drinking status, exercise, stress, and income level of all participants were determined by a questionnaire. Demographic and anthropometric data were collected. Fasting blood samples were collected to determine the serum levels of glucose, insulin, total bilirubin, total cholesterol, high-density lipoprotein cholesterol, and triglycerides. The presence of chronic gastritis was defined as a confirmed diagnosis by a physician. Food consumption was determined using a semiquantitative food frequency questionnaire. We found 8 different single nucleotide polymorphisms (SNPs) that are significantly different between subjects without gastritis and those with gastritis. Of these 8 SNPs, 3 SNP (rs17183225 [C/T], rs17780814 [A/C], and rs17780820 [A/G]) are closely located in the intronic region of zinc transporter *SLC39A11*, commonly known as *ZIP11*, and show linkage disequilibrium (D' = 1.0). We also found that participants with (TCA + TCG) haplotype of *ZIP11* at high levels of dietary intake of spicy foods show a significantly increasing tendency in the odds of having chronic gastritis when compared with those with CAA haplotype (odds ratio, 2.620; 95% confidence interval, 1.207-5.689). The data indicate positive associations between higher meal frequency and lower spicy food preference and gastritis. In conclusion, we found that zinc transporter gene *ZIP11* is associated with chronic gastritis in the Korean population and it may interact with spicy food, which suggests *ZIP11* as a therapeutic target for precision nutrition.

Abbreviations: *AFAP1L1*, actin filament associated protein 1 like 1; *ASTN2*, astrotactin 2; BMI, body mass index; CI, confidence interval; *LINC02147*, long intergenic non-protein coding RNA 2147; OR, odds ratio; SQFFQ, semiquantitative food frequency questionnaire; *SLC39A11*, solute carrier family 39 member 11; *SLIT2*, slit guidance ligand 2; SNP, single-nucleotide polymorphism; *ZIP11*, zinc transporter 11 precursor.

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1. Introduction

Nutrition is essential for supporting human life and it influences all biochemical processes that govern human health. Previously, nutritional research focused on determining the adequate intake of nutrients to maintain health and to prevent nutritional deficiencies. Because manifestation of a disease is not the result of the presence of a particular gene or mutation, but the result of complex interactions of the human genome with environments, today, the focus of nutritional research has shifted toward determining mechanistic details of molecular function of nutrition and elucidation of the interplay between genes and nutrients. Hence, the terms “nutrigenomics” and “nutriepigenomics” have emerged [1-3]. Nutrients influence the expression and the function of a gene at the transcriptional as well as at the translational and posttranslational levels so as to predispose the individuals to diseases [4,5]. Natural selection and other evolutionary processes mediated by food choices have likely played important roles in generating both human genetic diversity and orally transmitted cultural diversity. For example, agrarian populations like Asians have a longer length of the intestine because of consumption of vegetables and grains as their main staple foods, and cuisine has evolved to fit the inhabitants of a particular landscape over the last several millennia. The reason why some ethnic populations like spicy foods while the other populations do not like spicy foods is the distribution of particular chili peppers, and ethnic people continue to change the frequency of chili pepper use in their traditional recipes [6]. Previous studies reported that frequent users of spicy foods have been adapted by rating the oral pungency as less intense and a more pleasant taste [7,8].

Chronic gastritis is one of the most common lifelong, serious, and insidious illnesses in human beings. More than half of the world’s population is affected by this disease [9,10]. Although the role of gastritis in the pathogenesis of peptic ulcer and gastric cancer is firmly established, the significance of chronic gastritis as a serious disease is largely underestimated [11-15]. It was not until the year 1982 when *Helicobacter pylori* was discovered by Warren and Marshall [16] and they showed that this bacterium is the major cause of gastritis. In addition to genetic differences, environmental factors, such as diet or nutrition, are important components of gastric environment. Intake of nutrients influences the gastric environment, and epidemiologic studies have revealed that intake of green tea, fruits, or vegetables high in carotenoids, folates, vitamin C, and phytochemicals is protective against gastric cancer risk [17-19]. Conversely, high intake of red meat and/or processed meat and preserved foods high in salt and transition metals is associated with increased risk of gastric cancer [20,21]. The central role played by zinc in cell growth and differentiation has been explained in the gastrointestinal tract mucosa and the immune system. The antioxidant role of zinc in protecting human cells from apoptosis has been involved in chronic inflammatory diseases of the gastrointestinal tract, and the role of zinc carriers like Zn transporters in the gut has been emphasized in human studies [22,23]. The function of zinc transporter is influenced not only by the amount of zinc present in foods but also by other food nutrients such as cadmium or copper [24,25]. The zinc content in food is variable, and red meat is the richest common source of readily available zinc, providing 50% of dietary zinc in most of the people, and zinc bioavailability in the gastrointestinal tract is also influenced by the interaction between zinc and other nutrients present in foods [26,27].

The essential role of Zn in the immune system has been established [28]. However, the genetic effects and molecular mechanisms of Zn in the immune system, especially inflammation, have not been elucidated. Gastrointestinal tract is primarily responsible for Zn absorption and distribution through the body. Thus, we hypothesized that *ZIP11* variants would be important risk factors for chronic gastritis and that there would be an interaction effect of the relationship between their variants and spicy food intake on the development of chronic gastritis. The hypothesis was tested in 8840 Korean adults in the Ansung and Ansan cohorts of the Korean Genome and Epidemiology Study.

2. Methods and materials

2.1. Subjects

Samples and data were obtained from the Ansung and Ansan cohorts of the Korean Genome and Epidemiology Study in 2001. Among the 8840 patients who were aged 40 to 69 years and resided in rural and urban areas of Ansung City and Ansan City, 1686 men and 2448 women who responded to the survey of chronic gastritis and food frequency questionnaire were included in this study. The Korean Genome and Epidemiology Study protocols were approved by the institutional review board of the Korean National Institute of Health and the Keimyung University (approval no. 40525-201 511-BR-96-02). Informed consent was obtained from each subject on a written form. All subjects had lived in the area for at least 6 months and were free of any serious disease. The study was carried out in accordance with the recommendations of The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [29].

2.2. Basic characteristics of subjects

Interviews were conducted to determine the age, sex, education, smoking and drinking status, exercise, stress, and income level of all participants. Demographic and anthropometric data were collected by measuring the body weight and height in subjects who wore light clothing without shoes. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). Subjects were categorized into 3 groups according to the obesity references for Asian population: lean (BMI $<$ 18.5), normal (18.5 $\leq$ BMI$<$ 25), and obese (BMI $\geq$ 25) [30]. Education of the participants was divided into less than high school, high school, and college and more. Smoking status was defined as current smokers who had smoked more than 100 cigarettes in the past 6 months [31]. Exercise was defined as participation in moderate exercise (slow swimming, doubles tennis, volleyball, or occupational or recreational activity