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Genetic variations in taste perception modify alcohol drinking behavior in Koreans

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ABSTRACT

The sensory components of alcohol affect the onset of individual's drinking. Therefore, variations in taste receptor genes may lead to differential sensitivity for alcohol taste, which may modify an individual's drinking behavior. This study examined the influence of genetic variants in the taste-sensing mechanism on alcohol drinking behavior and the choice of alcoholic beverages. A total of 1829 Koreans were analyzed for their alcohol drinking status (drinker/non-drinker), total alcohol consumption (g/day), heavy drinking (≥30 g/day) and type of regularly consumed alcoholic beverages. Twenty-one genetic variations in bitterness, sweetness, umami and fatty acid sensing were also genotyped. Our findings suggested that multiple genetic variants modified individuals' alcohol drinking behavior. Genetic variations in the T2R bitterness receptor family were associated with overall drinking behavior. Subjects with the *TAS2R38* AVI haplotype were less likely to be a drinker [odds ratio (OR): 0.75, 95% confidence interval (CI): 0.59–0.95], and *TAS2R5* rs2227264 predicted the level of total alcohol consumption ($p = 0.01$). In contrast, the T1R sweet and umami receptor family was associated with heavy drinking. *TAS1R3* rs307355 CT carriers were more likely to be heavy drinkers (OR: 1.53, 95% CI: 1.06–2.19). The genetic variants were also associated with the choice of alcoholic beverages. The homo-recessive type of *TAS2R4* rs2233998 (OR: 1.62, 95% CI: 1.11–2.37) and *TAS2R5* rs2227264 (OR: 1.72, 95% CI: 1.14–2.58) were associated with consumption of rice wine. However, *TAS1R2* rs35874116 was associated with wine drinking (OR: 0.65, 95% CI: 0.43–0.98) and the consumption level ($p = 0.04$). These findings suggest that multiple genetic variations in taste receptors influence drinking behavior in Koreans. Genetic variations are also responsible for the preference of particular alcoholic beverages, which may contribute to an individual's alcohol drinking behavior.

1. Introduction

Alcohol is associated with more than 200 different human disorders, conditions, and injuries (Rehm & Shield, 2013), and excessive alcohol consumption is linked to approximately 2.5 million premature deaths each year (Rehm & Shield, 2013; Rothman, Greenland, & Lash, 2008). In contrast, low to moderate consumption of alcohol may benefit human health by reducing the risk of ischemic diseases (Lee et al., 2015; Roerecke & Rehm, 2012) and diabetes (Shi et al., 2013) through improvements in the blood lipid profile (Vu et al., 2016). These findings support the notion that alcohol consumption is a critical modifying factor of human health outcomes and quality of life. Therefore, factors that contribute to the formation of alcohol drinking behavior are of strong interest to those in research, clinics and industry.

Alcohol consumption and drinking patterns are determined by multifactorial traits, including sex, income, education and psychological and genetic factors (Cyders et al., 2016; Yusuf & Leeder, 2015). In addition, sensory components, including the perceived

Abbreviations used: ANOVA, analysis of variance; HWE, Hardy-Weinberg equilibrium; NCC, National Cancer Center; QC, quality control; SNP, single nucleotide polymorphism; *TAS1R1*, T1R1, taste 1 receptor member 1; *TAS1R2*, T1R2, taste 1 receptor member 2; *TAS1R3*, T1R3, taste 1 receptor member 3; *TAS2R4*, taste 2 receptor member 4; *TAS2R5*, T2R5, taste 2 receptor member 5; *TAS2R38*, T2R38, taste 2 receptor member 38; *TAS2R49*, T2R49, taste 2 receptor member 49; *TAS2R50*, T2R50, taste 2 receptor member 50.

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taste, the olfactory components of flavor and the temperature of the alcohol, are also thought to influence consumption (Dotson et al., 2008). Ethanol evokes a series of tastes: bitter, sweet, sour and salty (Allen, McGeary, & Hayes, 2014). A burning or stinging sensation is also caused by alcohol consumption, although these responses are relatively minor (Green, 1987). The intensity of these sensory responses varies across individuals; therefore, differential sensitivity and preference for alcohol taste may influence an individual's alcohol drinking behavior (Barber & Grichting, 1987; Lanier, Hayes, & Duffy, 2005; Moore & Weiss, 1995).

The oral sensation of taste is mediated by taste receptor proteins. Alterations in the genomic sequence of a taste receptor may cause a functional change in a protein, which may lead to differential sensitivity and preference for a certain taste. Therefore, genetic variations in taste perception mechanisms lead to differences in dietary intake and alcohol consumption (Dinehart, Hayes, Bartoshuk, Lanier, & Duffy, 2006). For example, taste 2 receptor member 38 (T2R38, *TAS2R38*) is a chemosensing protein that mediates bitter taste. The diplotype of the *TAS2R38* gene consists of three variants (A49P, A262V and V296I) and has been associated with dietary intake of vegetables and alcohol and tobacco consumption (Choi et al., 2017; Hayes et al., 2011; Lipchock, Mennella, Spielman, & Reed, 2013; Ramos-Lopez et al., 2015; Wang et al., 2007). Other genes in the *TAS2R* family, including taste 2 receptor member 13 and taste 2 receptor member 16, have also been shown to be associated with differential sensitivity for alcohol and alcohol drinking behavior (Allen et al., 2014; Dotson, Wallace, Bartoshuk, & Logan, 2012; Hinrichs et al., 2006; Wang et al., 2007). However, these findings regarding genetic variations in taste and alcohol intake were derived from a relatively small cohort, which hardly included the Asian population. Additionally, these experimental studies were conducted using only ethanol/scotch diluted in an aqueous solution (Allen et al., 2014; Brasser, Norman, & Lemon, 2010; Hayes et al., 2011). These studies examined the sensitivity to certain concentrations of sampled alcohol, with genetic variants as a modifying factor. However, ethanol is generally consumed as an alcoholic beverage and not as ethanol alone in an aqueous solution. Because alcoholic drinks commonly contain a series of active tasting molecules, including sugars, acids, proteins and other polysaccharides, and the aromatic compounds in wine, beer, and liquor may mask/enhance the bitterness and strength of alcohol itself (Allen et al., 2014; Heymann & Ebeler, 2016, pp. 88–89). Furthermore, the temperature of drinks and other sensory chemicals added to alcoholic beverages may trigger negative responses (irritation) to alcohol (Allen et al., 2014; Caterina, Rosen, Tominaga, Brake, & Julius, 1999; Tominaga et al., 1998; Trevisani et al., 2002). Therefore, an individual's preference for a certain taste or food may influence their choice of alcoholic drink, which may eventually contribute to an individual's alcohol drinking behavior and total alcohol intake. However, the association between genetic variants and the consumption of common alcoholic beverages has been poorly described (Hayes et al., 2011). Thus, a genetic taste study that incorporates the consumption of alcoholic beverages may improve our understanding of the role of genetic variants in human drinking behavior.

This study hypothesized that taste-related genetic variants might influence the alcohol drinking behavior of Koreans. After a review of the literature, 21 single nucleotide polymorphisms (SNPs) in various taste perception genes were selected. To better estimate the hypothesis, we evaluated the association between genetic variations with 1) alcohol drinking (drinkers/non-drinkers), 2) total alcohol intake (g/day, among drinkers) and 3) heavy drinking ($\geq$30 g/day, among drinkers). We also examined 4) the influence of genetic variations on the consumption of alcoholic beverages with two additional approaches: 4-a) the association with the choice of alcoholic beverage (drinkers/non-drinkers for each type of alcoholic drink, only among the drinkers) and 4-b) the intake of alcoholic beverages among the genotypes (ml/day).

2. Materials and methods

2.1. Subject recruitment and descriptive data collection

This study was conducted as a part of gastric and colorectal cancer research projects performed at the National Cancer Center (NCC) of Korea between October 2007 and December 2014. The participants were recruited from individuals who visited the Center for Cancer Prevention and Detection at the NCC to obtain a health screening examination (a benefit program of the National Health Insurance). The volunteers were asked to complete a self-administered questionnaire. The questions were designed to obtain each participant's demographic (e.g., age and sex), anthropometric data (e.g., height and weight) and medical history. Among the volunteers, 2024 subjects were selected and genotyped if they met the following inclusion criteria: free of systemic or mental disorder symptoms, free of diabetes mellitus and no history of any cancers within the past five years. Among these individuals, 195 participants were excluded because their genotype data were not suitable for quality control (QC) or the drinking status data were incomplete; therefore, 1829 subjects were finally included in the study. Ethics approval for the research was granted by the Institutional Review Board (approval number: NCCNCS-11-148 and NCC2015-0202). Informed consent was obtained from the participants prior to the study commencement, and all study procedures were performed following approved protocols.

2.2. Data collection for alcohol drinking behavior

The data for the participant's alcohol drinking behaviors were collected using a questionnaire. The subjects were requested to provide one of three choices to describe their drinking status: current, past or never drinker. If the participants defined themselves as a current or past drinker, then they were asked to quantify the frequency of alcohol consumption (one, two to three or four to six times a day, week or month), the amount of alcoholic beverages consumed on a typical day when they are drinking (by glass), and the type of alcoholic beverage consumed (beer, Soju, spirits, rice wine and wine) (see Supplementary Material 1 for the details on the questions). These five types of alcoholic beverages were chosen because they are the most commonly consumed alcoholic drinks in Korea (see Supplementary Table S1 for the details on the examined drinks); however, the subjects could still report their typical alcoholic drink if it was not included among the alcoholic beverages presented. Total alcohol consumption (g/day) was estimated from the frequency of drinking, the amount consumed (ml), the ethanol content of each drink and the specific gravity of ethanol (0.79) (see Supplementary Material 2 for the formulations and procedure to estimate the daily alcohol intake). The level of alcohol drinking was evaluated as light or heavy drinking. Heavy drinking (heavy drinker) was defined as subjects who defined themselves as drinkers and consumed more than 30 g/day of alcohol; consuming <30 g/day was defined as light drinking (light drinker). To estimate the association between the genetic variations and drinking behavior for each type of alcoholic beverage, the intake levels of those alcoholic drinks were calculated using the frequency of drinking and the total amount of alcoholic beverages (ml) consumed on each occasion, and not only the alcohol content, because other tasting and flavoring compounds in drinks may influence consumption.

The study focused on the association between taste-related