보건학 박사학위 논문

Determinants of Personality and Its Association with Risky Health Behaviors

성격의 결정요인과 성격 유형이 위험 건강행동에 미치는 영향

2017년 2월

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Abstract

Personality plays an important role in almost every aspects of individual's psychosocial and physical health. Additionally, an individual's personality affects health by predisposing the person to a higher chance of developing specific health behaviors. Attention to personality trait in clinical interventions is stressed in many reported health behavioral theories.

Temperament and Character Inventory (TCI) is a comprehensive personality inventory that is widely used in behavioral genetics. The original theory suggested that temperament traits were under genetic influences, whereas character traits were gradually built by an interaction between temperaments and environment until early adulthood. Heritabilities of personality has been reported to be about 0.4 in average, but discrepancies in different ethnicities are present, and these estimates tend to be inflated when only twins are used in the study. Also, despite moderate heritability of 0.3-0.6 for most personality domains, even large powered studies with Caucasian samples were not successful in locating specific genetic variant that explains personality. Besides identifying the determinants of personality, confirming its relationship to risky health behaviors, specifically with behaviors that are theorized to have psychosocial base, may give important public health implications. Additionally, personality may mediate the effects of gene on these health behaviors.

This study attempted to evaluate TCI by examining the genetic and

environmental contributions to personality with particular attention to spousal effects. Also, a genome-wide search for both TCI domains and multivariable TCI-Five-Factor Model (FFM, for sub-samples) were conducted in a population cohort of Korea, where cultural environments are different from Western populations. Lastly, individual personality traits or their linear combinations were tested for associations with health behaviors, such as eating behaviors, nicotine dependency, and alcohol dependency. Interacting effects between personality and genetic variants, which are reported to be related to psychosocial traits, on these health behaviors were explored.

This study includes a total of 3,479 individuals (1419 men, 690 families, 552 monozygotic twins, 119 dizygotic twins) from the Healthy twin study of Korea with detail epidemiologic, clinical information and TCI measures. Intraclass correlation coefficients (ICCs) and heritability were calculated to examine the genetic and shared environmental contributions to personality. Among these participants, 3,428 subjects with TCI measures were included in the univariate genome-wide association test. A total of 1,169 individuals (476 men) also fulfilled the FFM measures. Two platforms (Affymetrix Genome-Wide Human array 6.0, Illumina Infinium Humancore Beadchips) were used for genotyping and the markers were imputed using 1kG Asians. For univariate analysis, a family-based association test using mixed-effect variance component approach was conducted. For multivariable analysis of TCI-FFM model, multiple family-based quasi-likelihood score test (MFQLS) was performed to estimate the association of genetic variant to

multiple phenotypes in linear mixed model. Linear association was tested for TCI traits and health behaviors adjusting for age, gender, education, income level, and familial correlation. For health behavior traits, Dutch Eating Behavior Questionnaire (DEBQ, n=3,444), Fagerstorm Test for Nicotine Dependence (FTND, n=1,192), and Alcohol Use Disorders Identification Test (AUDIT, n=2,431) were measured. Factor Analysis on particular personality traits (novelty seeking (NS), self-directedness (SD), Cooperativeness (CO)) that were commonly observed to be associated with the targeted health behaviors were conducted using principal axis analysis, and the identified personality patterns were also tested for associations with health behaviors. A total of 183 genetic variants that were reported to be related with neuro-psychological traits were tested to see if they have gene-by-personality (GxP) effect on the health behaviors.

Moderate genetic contributions (0.15-0.44) were found for all TCI traits along with the evidence of shared environment (0.12-0.29) for harm avoidance (HA) and all characters. The ICCs of TCI in MZ pairs ranged 0.36-0.45. Spouses' had little resemblance for temperament, whereas for character dimensions, spouses (0.27-0.38) were more similar than first degree relatives (0.10-0.27). Resemblance between spouses increased with duration of marriage for most characters and HA. When the growing similarities between spouses were compared with their MZ cotwins' for subgroup of 84 trios, self-directedness (SD) of character showed even more similarities toward their spouses than cotwins as partnership duration increased (r=0.29). Univariate

TCI domain analysis CO domain were associated with ADAMTS17 gene (Chromosome 15, p= 9.0e-8), but other domains did not reach genome-wide significance level. For agreeableness of FFM, CDH13 gene (Chromosome 16, p=2.8e-7) had marginal p-value, and the same variant had association with agreeableness in previous reported study (p=0.046). In multivariate analysis, SD (TCI) and neuroticism (FFM) showed significant genetic associations in RP11-274B18.4 gene (r=-0.56, Chromosome 9, p= 7.52e-9). All seven TCI traits showed association with some targeted behaviors. Among them, combination of high NS, low SD, and low CO was observed in emotional eating, external eating, nicotine dependence, and alcohol dependence. The subscales of these traits were factorized to obtain specific personality profile named Vulnerability, and its association with, as well as its' ability to predict risky health behaviors was also observed. SNAP25 gene interacted with self-transcendence in its association to emotional eating, EVL gene interacted with SD on effect of external eating, and CACNA1C gene interacted with CO to affect FTND.

The findings with regard to change in SD into late adulthood support the psychobiological theory of temperament and character, which suggests that both personality domains have distinct developmental trajectories despite equally large genetic influences. Also novel genetic loci were found to be associated personality traits, particularly in character dimensions. The findings from genome-wide search for associated gene illustrates that there may be different biological background in Koreans, and that a multiple

measures of personality traits might better capture the genetic architecture of personality traits. Lastly, by finding the personality patterns and GxP effects that have shown increased risk in developing certain health behaviors, translating them into personalized medicine for effective prevention and intervention for risky health behaviors is possible.

Keywords: Personality, Genetic Epidemiology, Heritability, Genome-Wide Association study, family-based association study, Gene-by-Personality interaction, Health behaviors, Personalized Medicine

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Abbreviations (Alphabetical Order)

AUDIT: Alcohol Use Disorders Identification Test
AUDIT-C: Alcohol Use Disorders Identification Test consumption questions
BMI: Body Mass Index
CI: Confidence Interval
CO: Cooperativeness
DEBQ: Dutch Eating Behavior Questionnaire
DZ: Dizygotic
EME: Emotional Eating
EXE: External Eating
FDR: False Discovery Rate
FFM: Five Factor Model
FTND: Fagerstorm Test for Nicotine Dependence
GWA: Genome-Wide Association
GxE: Gene by Environment Interaction
GxP: Gene by personality interaction
HA: Harm Avoidance
ICC: Intraclass Correlation
LD: Linkage Disequilibrium
MAF: Minor Allele Frequency
MZ: Monozygotic
NS: Novelty Seeking
PCA: Principal Component Analysis
PE: Persistence
PY: Pack-Year
Q-Q: Quantile-Quantile
RD: Reward Dependence
RSE: Restrained Eating
S.D.: Standard Deviation
S.E.: Standard Error
SD: Self-Directedness
SNP: Singe Nucleotide Polymorphism
ST: Self-Transcendence
TCI: Temperament and Character Inventory

I. Introduction

1. Background

1.1 Definition of Personality

The scientific question of assessing the extent of genetic and environmental influences on individual's personality is essential in understanding the basis of human health. Personality traits are reported to be associated with not only psychological traits, but also physical conditions [1-3], and plays an important role in shaping individual's lifestyle and attitude towards their environmental surroundings.

The concept of personality has been theorized ever since the age of ancient Greeks. For instance, Hippocrates (400 B.C.) claimed that different types of personality are caused by components of bodily fluids. His idea that personality is based on different biological characteristics of individuals are resonated in modern psychology [1, 4]. Since then, many experts in psychology have tried to define and dissect the basis of personality. A classical definition of personality is "a dynamic organization, inside the person, of psychophysical systems that create the person's characteristic patterns of behavior, thoughts, and feelings" [5]. Additionally, Larsen and Buss (2008) defined personality as "the set of psychological traits and mechanisms within the individual that are organized and relatively enduring and that influence his or her interactions with, and adaptions to, the intrapsychic, physical, and social environments" [6] In both definitions, it is emphasized that individual's personality influences and interacts with almost every facets of life, consecutively affecting one's psychophysical health.

1.2 Measurement of Personality – Temperament and Character Inventory

There are two key assumption in the theory of personality traits or the ‘true nature’ of personality that defines one’s core; it needs to be relatively stable over time and directly influence one’s behaviors [7]. Individual’s personality needs to be summarized into small number of factors that represent basic dimensions of personality, and these traits should stably measure the variations in the basic ways of response to certain situations or stimuli [8, 9], and predict individual’s behaviors or actions.

Many researchers have tried to explain individual personality as a set of cross-culturally reproducible traits, and developed inventories to assess these theoretical models. Of the many developed inventories explaining personality, Cloninger’s Temperament and Character Inventory (TCI) [10, 11] is commonly used in behavioral genetics because it distinguishes between temperament traits that are emotion-based and developmentally stable on average, from character traits that develop in a stepwise fashion toward socially-favored norms [12]. When compared to other multi-dimensional inventories, the validity of the TCI is as great as or greater than others, showing particular strength in measuring healthy maturation of character [11].

There are seven dimensions in current version of TCI [13, 14]. This taxonomy measures four dimensions of temperament; novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (PE) [13, 15, 16]. Using the temperament dimensions, one can distinguish subtypes of personality disorders, but temperaments did not specify whether or not an

individual have a healthy personality or a personality disorder by itself. Therefore, a second domain of personality described as “character” was also proposed in order to measure individual differences in achieving their goals and values intentionally, reflecting the important influence of socio-cultural environment on development of one’s character [17]. Three dimensions of character are as follows; self-directedness (SD), cooperativeness (CO), and self-transcendence (ST).

The original theory by Cloninger claimed that temperament and its components are mainly genetically or biologically determined with distinct biological basis of specific neurotransmitter responses. NS was proposed to be influenced by dopamine as an expression of a behavioral activation system. Theoretically, HA was influenced by serotonin, which acts as a behavioral inhibition system. RD was proposed as a dimension of behavioral maintenance system influenced by norepinephrine. Lastly, PE was claimed as a behavioral extinction system involving glutamate interacting with other neurotransmitters [14, 18, 19].

In contrast, character traits were hypothesized to change with the age and maturation, and were thought to be strongly affected by the surrounding psychosocial environments and education; SD, as the executive component of an individual’s mental self-government; CO, the legislative aspect of mental self-government, allowing people to act according to principles; ST, the judicial aspect of self-government, allowing insight into when rules apply through awareness of a person’s connections to the world as a whole [13].

According to Cloninger's original hypotheses, genetic variations were expected to be fundamental for temperament development, whereas social norm-favoring to be more important for character. However, current theory considers the distinction between temperament and character to be based on differences in the type of learning regulated by different domains. Temperament is regulated by individual differences in behavioral conditioning whereas character is regulated by individual differences in semantic learning and self-aware consciousness [20, 21].

As emphasized above, individual differences in personality have major significance for almost all aspects of health, including physical, mental, and well-being in social aspects [22]. Cluster C personality disorders, such as obsessive-compulsive disorders are related to high anxiety proneness (i.e., high HA); Cluster B disorders, like antisocial or borderline disorders, to impulsivity (i.e., high NS), and Cluster A disorders (paranoid, schizotypal) to social aloofness (i.e., low RD) [2, 21]. Personality is also strongly involved in susceptibility to stress and physical disorders related to lifestyle, including heart disease [3, 23], and obesity [24, 25].

Low or high scores of character dimensions have also been associated with personality disorders. Lower SD score showed strong relationship with presence of personality disorders [26]. Low CO score was also an independent predictor of all types of personality disorder clusters, whereas high ST score suggested moderately increased risk of schizotypal and Cluster B personality disorders [27, 28].

1.3 Measurement of Personality – Five Factor Model

Another personality taxonomy used widely in behavioral research is the NEO Personality Inventory (NEO PI-R) [29, 30] that defines the Five Factor Model (FFM) or Big Five personality traits. This theory describes the personality in five broad factors named openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism. Openness to experience is characterized by general appreciation for variety of experience. Conscientiousness is related to self-disciplines and how individuals control or regulate themselves. Extraversion measures the likelihood of a person to engage in breadth of activities, and extrovert individuals tend to be energetic, enthusiastic, and action-oriented. Agreeableness trait represents social harmony, and agreeable individuals generally are helpful, kind, and considerate. Lastly, neuroticism is a trait that measures negative emotions or emotional instability. Individuals with high scores of neuroticism are more likely to experience frustrations and stress [31]. The FFM is reported to represent dimensions of both normal and abnormal personality [32]. Especially, high neuroticism and low agreeableness were consistently observed in different types of personality disorders [33].

1.4 Genetic studies on Personality

Given the influence of personality traits on a wide range of human behaviors, understanding the contribution of genes and environments to variation in personality traits is an important topic of interest.

Previous studies on the extent of genetic contributions to personality have reported that all personality traits measured by TCI are influenced by genes to varying degrees, depending on the study [34-37]. A Japanese study reported that TCI's additive genetic factors ranged 0.22 ~ 0.49 and both character and temperament traits showed a substantial genetic influence. However, despite the evidence of non-additive genetic effects on personality (dizygotic (DZ) twin's correlation being lower than half of monozygotic (MZ) twin's correlation), only PE showed a significant non-additive estimate of 0.37 [35]. A study of temperament traits of Caucasians in Australia found broad-sense heritabilities of 0.53~0.56 with the evidence of a non-additive genetic component ranging 0.11~0.35 [36]; a subsequent study showed that character traits were also as heritable [37]. Studies using Five Factor Model (FFM) [30] reported similar findings with the additive component ranging 0.36~0.61 [38, 39]. A recent meta-analysis on the heritability of personality reported that the average effect size was 0.40, which in other words, genetic contributions to variation in persoanlity is accounted for about 40% [40].

However, some points that are reported are not consistent and need replications. In particular, the genetic influence in terms of heritability has been estimated to be lower in Asians than Caucasians. Additionally, for TCI, it is not clear whether Cloninger's distinction between temperament and character is adequately supported by empirical results. Most studies dissecting personality traits have been carried out in studies that compare only MZ and DZ twins, which has an advantage over studies with singletons because they

assure close comparability of “shared environments” for twin pairs, who are born at the same time, share intrauterine environment, and are reared together. On the other hand, heritability estimates from twin studies tend to be inflated because of difficulty distinguishing additive and non-additive genetic effects in MZ twins [40, 41]. Therefore, carrying out a study including both types of twins and other family members, including spouses is required to more reliably discriminate the sources of family resemblance, such as assortative mating and specific environment shared by variety of family relationships. Other than the genetic effects, shared environment between family members, age, culture, socioeconomic status, and etc. are reported to contribute to differences in some aspects of personality [42, 43].

Despite the evidence of moderate heritability, finding specific genetic variants that explain the variances in personality have been elusive in studies with Caucasian samples. A large-scale meta genome-wide association (GWA) study with over 11,000 individuals was unsuccessful in discovering any single nucleotide polymorphism (SNP) associated with temperament scales of TCI [44], and another meta-analysis study on FFM reported two significant SNPs related to openness to experience and conscientiousness, but failed to replicate the results [45]. A recent genome-wide meta-analysis of FFM in Korean cohorts, which was the first East-Asian meta-study, also reported several variants that are suggestive to be associated with personality traits, but none of them were genome-wide significant [46]. Also a very recent study with more than 70,000 subjects of European ancestry conducted a meta-

analysis searching for the genetic variant that is associated with extraversion [47] and neuroticism [48]. The investigators were not able to find a genome-wide significant SNP for extraversion, but *MAGI1* gene (rs35855737) that is expressed in human's neuronal tissue was significantly associated with neuroticism. However this study was not successful in replicating the result. The authors concluded that increasing the number of subjects is necessary in order to acquire a sufficient power to detect the novel locus for personality. Also they emphasized that personality may be influenced by many number of variants with small effect sizes [47, 48]. Vinkhuyzen et al. (2012) also reported that the common SNPs only explain a small portion of the variances in personality and heritability estimated from reported pedigrees. This "missing heritability" phenomenon might be explained by biased estimation of heritability confounded by non-additive genetic factors, whereas SNPs only estimate additive genetic effects. Also, the effect of rare variants that cannot be addressed by typical GWA studies should be considered [49]. The summary of the reported GWA studies are presented in sTable 1.

Despite lack of success in finding the genetic variants that explain moderate level of heritabilities of personality traits, many approaches not limited to large-scale consortium study, multivariable analysis, gene-by-environment interaction (GxE) analysis, and etc. should be applied in the search for biological backgrounds of personality.

1.5 Health Behaviors and Personality

Risky health behaviors such as tobacco smoking, alcohol drinking, and unhealthy dieting are one of the main preventable causes of global mortality and morbidity. [50-53] Cigarette smoking was the leading cause of death in United States, accounting for 18.1% of death in 2000 [51], and caused more than 6 million premature death in a year [52]. Obesity, which is caused by unbalanced diet or low physical activity, accounted for 16.6% of death according to Mokdad et al. (2004), and in 2014, CDC reported that the age-adjusted obesity prevalence among American adults is about 35 % [53]. The Korea national health and nutrition examination survey of 2011 reported that 32% of Korean adults were obese [54], stressing the growing problem of "Globesity". Alcohol drinking is also an another important risk factor that attributes to morbidity and mortality in worldwide [55, 56].

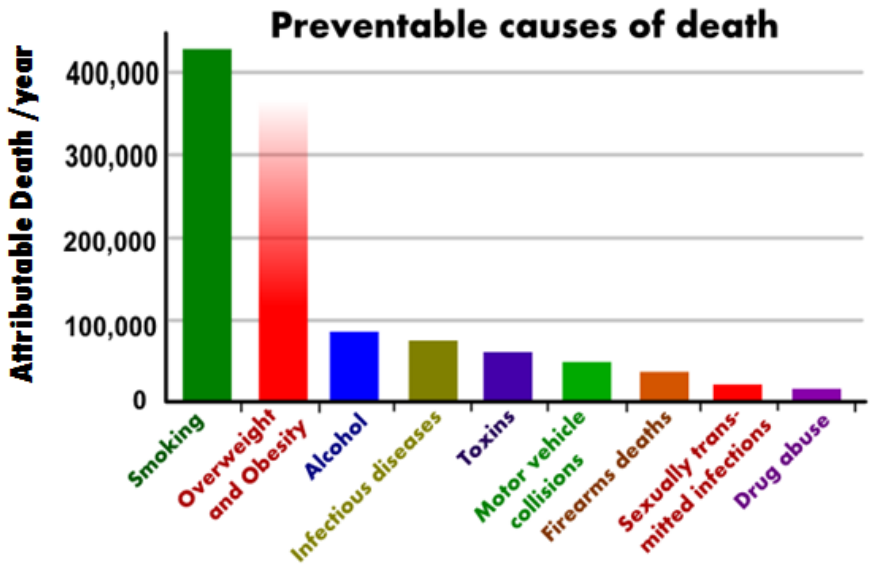


Figure 1.1. Attributable Death / year by preventable causes in the United States, 2000 -Adopted from Mokdad et al. (2004) [51]

In development of these specific risky health behaviors, an individual's personality plays an important role [57, 58]. There are many health behavioral model and theories already presented, explaining mechanism of occurrence or change in the health habits. The model in Figure 1.2 is the Health Belief Model presented by Becker in 1974 [59]. The Health Belief Model describes that through perceived susceptibility, severity, threats, benefits, and disability, possibility of behavioral change arises. In this model, personality is presented as one of the modifiable personal factors. Another health-behavior-related theory named Social Cognitive Theory [60] hypothesized that personal factors, environmental influences, and behavior itself affects each other reciprocally, and personality is emphasized as the personal factor in this model as well.

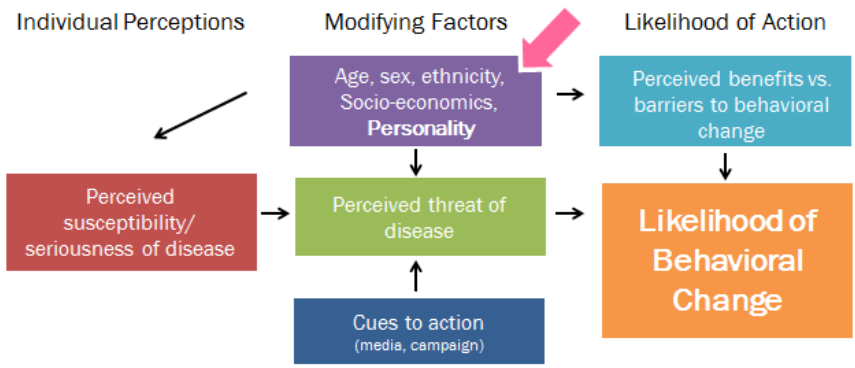


Figure1.2. Health Belief Model Theory adopted from Becker (1974) [59]

One of the main goals of public health is to organize health programs targeted for a population that are defined as "a set of planned and organized activities carried out over time to accomplish specific health-related goals and

objectives” [61]. In order to perform a health program planning, a PRECEDE-PROCEED model [61] was proposed (Figure1.3). This model is comprised of two set of phases which are assessments of factors in varieties of phases in an ecological model, and strategic implementation of interventions guided by the findings from the assessments. For the development of health modification programs that are either education-based approaches or policy regulations, investigating the relationship between epidemiological and ecological factors are essential. Personality can be considered as one of the predisposing factors, defined as “the values that facilitate or hinder motivation for change”, that directly affect behaviors, which in turn affect individual’s health.

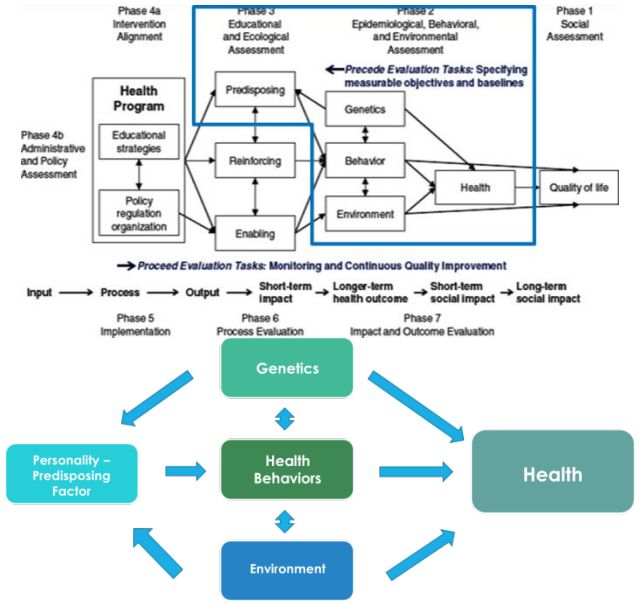


Figure1.3. PRECEDE-PROCEED Model [61, 62], and the framework of current study

Based on these philosophies, the overall framework of this study is derived from the PRECEDE-PROCEED model. Genetic and environmental

factors that contributes to individual's personality (predisposing factor) is assessed, followed by the assessment of personality's effect on health behavior, which then directly affects one's health and quality of life.

Personality traits have been proven to be the plausible prediction factors for health behaviors and health conditions in many studies. For instance, few studies reported that increased impulsivity, extraversion, and neuroticism is associated with smoking behaviors [63, 64]. Also it has been suggested that low conscientiousness shows relationship with risky health behaviors such as smoking cigarettes, excessive alcohol use, unhealthy eating, and etc. [65]. Additionally, HA and NS of TCI has been reported to predict tobacco use or alcohol addiction [66-68]. Further review on health behaviors and personality is discussed in Chapter 4. Despite its affirming relationships to health behaviors, personalized health promotion incorporating both individuals' personality characteristics and related gene has not been widely utilized yet.

1.6 Gene by Personality interaction (GxP)'s effect on Health Behaviors

With the rise of increased demands for patient-centered health care system, focus on unique individual preferences, values, genetic characteristics, and personality have been emphasized [69-71]. In the era of personalized medicine, it is especially important to focus on personality traits, which are relatively inexpensive to measure and essential in defining the unique characteristics of an individual. Personality traits may reflect biological systems that are related to health conditions or pathogenesis of a disease.

Differences in personality are also related to how individuals react differently to disease and cope with the stress. Likewise, it is known to be related to many different health behaviors that can promote or alleviate one's health [70].

As demonstrated in Figure 1.4, biological determinants such as individual genotype, or interaction between gene and environment (GxE) may play an important role in developing a specific health behavior and maintaining it, which effects the risk for developing certain health conditions [72]. In addition, gene and GxE can have direct effect on health outcomes. In the pathway of this model, intermediate phenotype, such as personality can be introduced. These intermediate phenotypes, which are partly biologically based, are considered to be more proximal to biological determinants of health than the health behaviors themselves [57, 73], and can mediate the effects of gene on health behaviors.

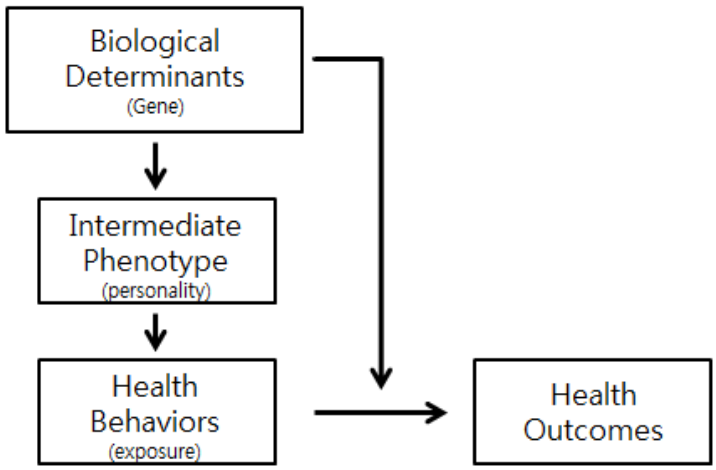


Figure 1.4. Personality as an intermediate phenotype of biological determinants on health behaviors and outcomes – adopted from [57, 72]

From this point of view, the concept of gene by personality interaction (GxP) effect on health behavior is introduced [57, 74-78]. Most of the reported studies on GxP are focused on neurotransmitter genes. For instance, a serotonin transporter gene (5-HTTLPR) was reported to have an effect on smoking motivations and nicotine dependence by interacting with neuroticism [79], which the results can be integrated into smoking prevention or cessation programs. Doran et al. (2013) published a study on the interaction of Dopamine D2 Receptor gene (DRD2 Taq1A, rs1800497) and impulsivity on smoking initiation [74]. Individuals with Taq1A+ genotype are known to have 30~40% reduced dopamine receptor density, resulting in low baseline dopamine tone. For these individuals, dopamine release after smoking cigarette will be more effective, and the authors reported that there was increased risk for smoking initiation especially for those with high impulsivity. Mediating effect of reward sensitivity and DRD2 Taq1A was also observed in patients with binge eating disorder and obesity [78]. Another study on DRD2 SNP (rs6276) suggested interacting effect with low SD on alcohol consumption among males [76], and in association of Aldehyde dehydrogenase 2 (ALDH2) and heroin addiction, heroin dependents with ALDH *1/*2 or *2/*2 had higher NS, suggesting personality's role as a mediator in these relationships [77]. The findings from these studies suggest that, with the measurements of personality and genotype of an individual, identifying the ones with high risk of developing certain behaviors related to health and well-being is feasible.

2. Objectives

From these backgrounds, there are several research questions that are targeted to explore in this study. First, how much does the gene and environment contribute to the variance of Korean's personality? Can we capture the discrepancies in the estimates between Caucasians and Asians? To what extent, does shared environment between various family types other than twins affect one's personality? Also, do personality traits change? With these questions, the aim of this study is to probe the biological basis of Cloninger's theory of temperament and character by estimating genetic contributions to personality traits and examining the influence of "shared environment". In order to precisely investigate different sources of resemblance across diverse relationships, multiple family relationship types were all systematically observed. This part of the study has been published in 2015, at the Journal of Psychiatric Research [80], and some updates will be discussed further in Chapter 2.

In the second part of this paper (Chapter 3), the focus will be on searching for the genetic variants that explain variations in personality of Korean population. With the elusive findings from previous studies with Caucasian samples and Korean Meta study on FFM, the aim is to conduct a genome-wide search for genetic variants that are associated with personality domains using Cloninger's TCI with different theory in measuring the individual's baseline personality from FFM. Also there will be more extensive search for biological backgrounds of personality with additional approaches,

such as incorporating multiple dimensions of personality in finding the novel locus and searching for replicative variants.

Thirdly, with the confirmation of genetic contribution to personality, the aim is to investigate the relationships between personality and health behaviors in Chapter 4, particularly health behavior traits that are related to alcohol, smoking dependence, and eating behaviors. These targeted risky health behaviors are established as the known causes of cancers, cardiovascular diseases, obesity, depression, and etc. Also, investigation of the gene-personality (G x P) effect on these health behaviors with genetic variants that are reported to be associated with neurotransmitters or psychological traits will be conducted in a population cohort of Korea, and discussion on how one can translate the results to health behavior prevention, modification or interventions integrating both individual's gene and personality will be done.

With the findings from this study, exploring the biological basis of personality and the utility of personality traits as a tool for health treatment, which are inexpensive and easily-accessible will be performed. Also the results can be integrated to personalized intervention strategies for modification of risky health behaviors, consecutively preventing and effectively treating related diseases.

II. Genetic and Environmental effect on Personality

1. Material and Methods

1.1. Participants

The Healthy Twin study has recruited adult like-sex twins using a nation-wide twin-family register since 2005. The detailed protocols and characteristics of study participants have been described previously [81, 82]. Individual twins and their first degree relatives who participated in this Healthy Twin study completed a set of epidemiological questionnaires, including inventories measuring psychosocial characteristics, and visited one of three medical centers across the country in order to complete a wide range of physical examination, in-depth clinical tests, and biochemical tests. A total of 3,479 individuals (1,419 men, 2,060 women, 690 families) from the Healthy Twin Study in Korea completed the TCI questionnaire. This study includes 552 MZ pairs (201 male and 351 female pairs) and 119 DZ pairs (52 male-male and 67 female-female pairs) (Table 2.1).

Table 2.1. Composition of monozygotic twins, dizygotic twins, and sibling pairs

		Monozygotic Twins	Dizygotic Twins	Sibling Pairs
Sex n (%)	Male pair	201(36.41)	52(43.70)	401(14.64)
	Female pair	351(63.59)	67(56.30)	1117(40.78)
	Opposite Sex pair	-	-	1221(44.58)

In order to ascertain the zygosity of samples, 16 short tandem repeat markers were used for 406 twin pairs. For the remaining twins, the zygosity

was determined using a self-administered zygosity questionnaire, which has >98% predictive value for MZ [83]. Twin pairs whose zygosity was inconclusive by the questionnaire alone were genotyped to confirm their twin types.

1.2. Measurements of Personality

The Korean version of Adult Temperament and Character Inventory-Revised-Short (TCI-RS) with a 140 items on a 5 point Likert scale was used [84] to measure the personality traits of participants. The survey was self-administered, and then was individually reviewed by an examiner when a subject visited any of the three recruiting sites; this resulted in minimal missing values. The scores were calculated by summing the values of responses either reversely or directly according to the protocol provided by the manufactures.

A written informed consent was obtained from all participants, and the study protocol was approved by the ethics committees at the Seoul National University, Samsung Medical Center, and Busan Paik Hospital.

1.3. Statistical analyses

The TCI scores were handled as continuous variables. Simple statistics and data handling were done using the SAS software (SAS Institute, Cary NC).

1.3.1. Familial Correlation

One way to measure the degree of familial resemblance is to estimate the familial correlation estimates [85, 86]. In this study, we especially focused on the resemblance of personality between specific family types of all possible relationships in a family. The intraclass correlation coefficients (ICC) within particular family pairs were calculated using a mixed model with proportions of the phenotypic variance between specific family groups, or the variance of random effect of specific family type, over the total phenotypic variance, adjusted for age and sex for non-twin pairs.

$$\frac{Var(\,Random\,Effect)}{Var(Total)} = \frac{Var(\,Random\,Effect)}{Var(\,Random\,Effect) + Var(\,Residual)}$$

The ICC of the various family relationship types with different genetic distances were analyzed; DZ, siblings, and parent-offspring pairs are all 1st degree relationship sharing 50% of the additive genetics on average, while MZ share 100% , and spouses share no genes identical by descent (IBD).

1.3.2 Dissection of the Resemblance between the Spouses

In order to dissect the effect of an adult environment, ICC of 432 spouse pairs, who had both TCI scores and marriage duration information available, were compared between the two groups which were divided according to their duration of marriage. To distinguish whether the trend is displayed due to an assortative mating or convergence of personality, the correlation coefficients of the partners' absolute score difference (ΔSP) and

marriage duration were calculated. The score absolute differences (ΔMZ) between MZ pairs were also correlated with their age.

In order to see whether the direction of the resemblance is skewed toward their cotwin (i.e., genetics) or their spouse (i.e., shared environments), the correlation of spousal relationship length and the base-2 logarithmic transformation of proportion of ΔSP over ΔMZ after adding a constant 10 to fix the negative values was computed for 84 subgroup individuals who had both their cotwin's and spouse's data available. If both twins' spouse information was available (25 trios), they were counted as two separate trios. The ΔSP /ΔMZ values were adjusted for random effect of MZ twins. Positive computed correlation values indicate trend toward spousal resemblance or less spousal differences as partnership gets longer.

The rationale of cotwin-spouse trio design is as following: 1) spouses share only environments, and spousal correlation should arise from the C (common environments), unless it is explained by the assortative mating. 2) MZ twins originally share both full genetics and early-life environments. After adulthood, however, the nature of shared environment changes, and less and less are shared. The study focus was on the shared environments which can influence the personality. Although MZ twins should share some degree of "environments" even after their respective marriage, it should be much less than what is expected when they live together in younger age. The MZ cotwin pairs, thus, serve as a "genetic" control. 3) Combining the cotwin and spouse trio matched individually will compare the two distinct directions of changes:

toward genetic destiny or environmental influence. The matched cotwin-spouse trio in adults or older people will be useful in showing whether later onset phenotypes are under the genetic or environmental influences. Cotwin resemblance, should be tested against their ages while the spousal correlation should be done against their marriage duration.

1.3.3 Heritability

Genetic heritability or the narrow-sense heritability is the proportion of the total phenotypic variance that is explained by the additive genetic components. In this study, to estimate the additive genetic and shared environment components of TCI, a variance decomposition method [87], with basic inheritance model of polygenic effect, was applied. In this model, the phenotype (P) is a function of genetic (G) and environmental (E) effects. Then, the total phenotypic variance can be expressed as the following.

$$V_P = V_G + V_E$$

If total genetic variance is divided by phenotypic variance, then the estimated proportion can be defined as the broad-sense heritability. Also, this genetic variance can be decomposed further into additive (A) and dominance (D) effects.

$$V_G = V_A + V_D$$

$$h^2{}_N = V_A/V_P$$

The proportion of variance of additive genetics over the total phenotypic variance is termed the narrow-sense heritability. Further, the environmental

variance can be also decomposed into common environment (C) shared by families and random (R) environmental effects.

$$V_P = V_A + V_D + V_C + V_R$$

The variance of C component, which is linear and additive, over the total phenotypic variance is interpreted as the contribution of shared familial environmental effect on phenotype.

$$c^2 = V_C / V_P$$

This variance component method was performed using SOLAR (Sequential Oligogenic Linkage Analysis Routines, Texas Biomedical Research Institute) package. With the advantage of using extended families and twins, precisely distinguishing the dominance genetic effects and incorporate various types of shared familial environment was probable [88]. To examine the shared environmental effects further, different types of environmental sharing within family were analyzed; household as a whole, where the effect on every family member is identical ("household model"); effect of siblings sharing the same parents, ("sibling effect model"); effect of being a partner ("spouse effect model") is estimated.

The variance of personality traits was decomposed into additive genetic (A) explained by genetic distance of family relationship, common environments (C) pertaining to cohabiting groups, and unique environmental components (E) comprising the residuals, assuming that A and C are independent (ACE model). Another model including non-additive, or

dominance genetic (D) component (ACDE model) was also fitted to incorporate more complex genetic effects for the scales with MZ ICC larger than the twice of DZ ICC. Heritability (h^2) was calculated as the proportion of the total phenotypic variance explained by additive genetic variance after accounting for the covariates of age, sex, and their interactions such as age^2, age-by-sex interaction, and age^2-by-sex interaction. The best fitting model was chosen from different nested explanatory models by comparing the Akaike's Information Criterion (AIC).

2. Results

Table 2.2 shows basic summary of TCI dimensions in the total study population. The average age of male participants was 44.47, whereas female's average age was 43.86. Mean values of all seven dimensions were significantly different between the genders, even for the weak effects due to large size of the sample. Average scores of NS, PE, and SD were higher in males, while HA, RD, CO, and ST were higher in females.

Table 2.2. Mean scores of the seven TCI dimensions of total population in this study, stratified across sex

	Men		Women		
	n	mean(S.D)	n	mean(S.D)	p value [a]
Age	1419	44.47(14.32)	2060	43.86(13.11)	0.20
Temperament					
NS	1407	29.99(9.67)	2033	27.46(10.42)	<0.0001
HA	1411	35.18(10.44)	2029	38.84(10.70)	<0.0001
RD	1406	41.41(7.95)	2025	42.75(8.53)	<0.0001
PE	1413	42.86(10.10)	2030	40.17(10.27)	<0.0001
Character					
SD	1410	46.70(10.18)	2035	45.20(10.40)	<0.0001
CO	1413	53.10(8.93)	2028	54.13(8.75)	0.001
ST	1406	24.22(11.31)	2034	26.07(11.40)	<0.0001

[a] obtained by Student's t-test
All rounded to the nearest tenth
Abbreviations: S.D, Standard Deviation; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence

Figure 2.1 shows the trend of TCI's seven dimensions by age groups, stratified by sex. Both men and women showed a similar trend in all of the dimensions, and average trait scores were broadly constant across different

age groups over 30 in six dimensions. However NS tended to decrease with age, and HA scores were significantly higher among women than men in most of the age groups.

The ICC of MZ twin pairs ranged from 0.36~0.45, 0.00~0.27 for DZ, 0.12~0.24 for DZ and sibling pairs combined, 0.08~0.27 for parent-offspring pairs, and 0.02~0.38 for spouse couples (Table 2.3). MZ pairs showed the highest ICC for all personality traits; DZ and sibling pair's ICC levels were generally similar to those of parent-offspring pairs. ST had the highest ICC in most of the relationships. The resemblance of spouses for temperament traits was low (0.02-0.10) whereas spouse resemblance for the three character dimensions was generally high (0.20-0.38), almost comparable to ICC of MZ twin pairs.

In order to distinguish the effects of assortative mating and adulthood environment, spouse pairs were divided according to their length of marriage with the cutoff at the 30 years. Marriage duration among the participants ranged 12~62 years with the average of 32 years. There were 176 pairs, whose length of marriage was less than 30 years, and 256 pairs reported that their marriage durations were longer than 30 years. When the ICC of these two groups were compared, estimate for HA was significantly increased from 0.00 (95% Confidence Interval (CI), 0.15-0.15) to 0.20 (95% CI, 0.08-0.32) and SD was significantly increased from 0.19 (95% CI, 0.05-0.33) to 0.33 (95% CI, 0.21-0.43). Other personality traits' ICC also showed increasing trend despite the statistical insignificancy. Interestingly, all ICC

estimates of character traits of couples with less than 30 years of marriage were all significant, and the level of the increased coefficient was larger than most temperament traits (Table 2.4).

The correlation coefficients of the ΔSP and relationship duration were significant for HA and SD; ΔSP decreased with the duration of partnership. ΔMZ showed no significant correlation with age. The matched fraction of log (ΔMZ/ΔSP) had a significant correlation with marriage length only in SD (r= 0.23, p-value=0.04), but not in HA. Note that a positive coefficient means more resemblance toward spouse's personality than the cotwin's (Table 2.5).

Evidenced by the more than twice the differences in ICC between MZ and DZ or pooled first-degree relationships (DZ+sibling), non-additive genetic variance was tested; the ACDE model was fitted to estimate the contribution of non-additive genetic components to phenotypic variations. NS, RD, and PE best fitted to the ADE model whereas HA, SD, and CO did to the ACDE model, when spouse effect model was used as shared environment component. ST best fitted to the ACE model where C is the effect of environment shared by spouses as well. The estimates of heritability ranged 0.15~0.44, highest for ST and lowest for PE. The effects of environment shared by spouses accounted for HA and all character traits (0.12~0.29) (Table 2.6). The non-additive genetic influences accounted for 0.12~0.28; HA and PE had higher D component than A, indicating important contribution of complex genetics on these traits. Except for HA and character traits, shared

environmental effects were negligible when dominance genetic effects were considered in the best fitting models.

Age and sex explained 15% of NS's variation whereas all other traits' variance due to age and sex were less than 5%. This is consistent with the findings from Figure 2.1.

Figure 2.1. Trend of average TCI trait scores and their 95% confidence intervals by age groups and sex

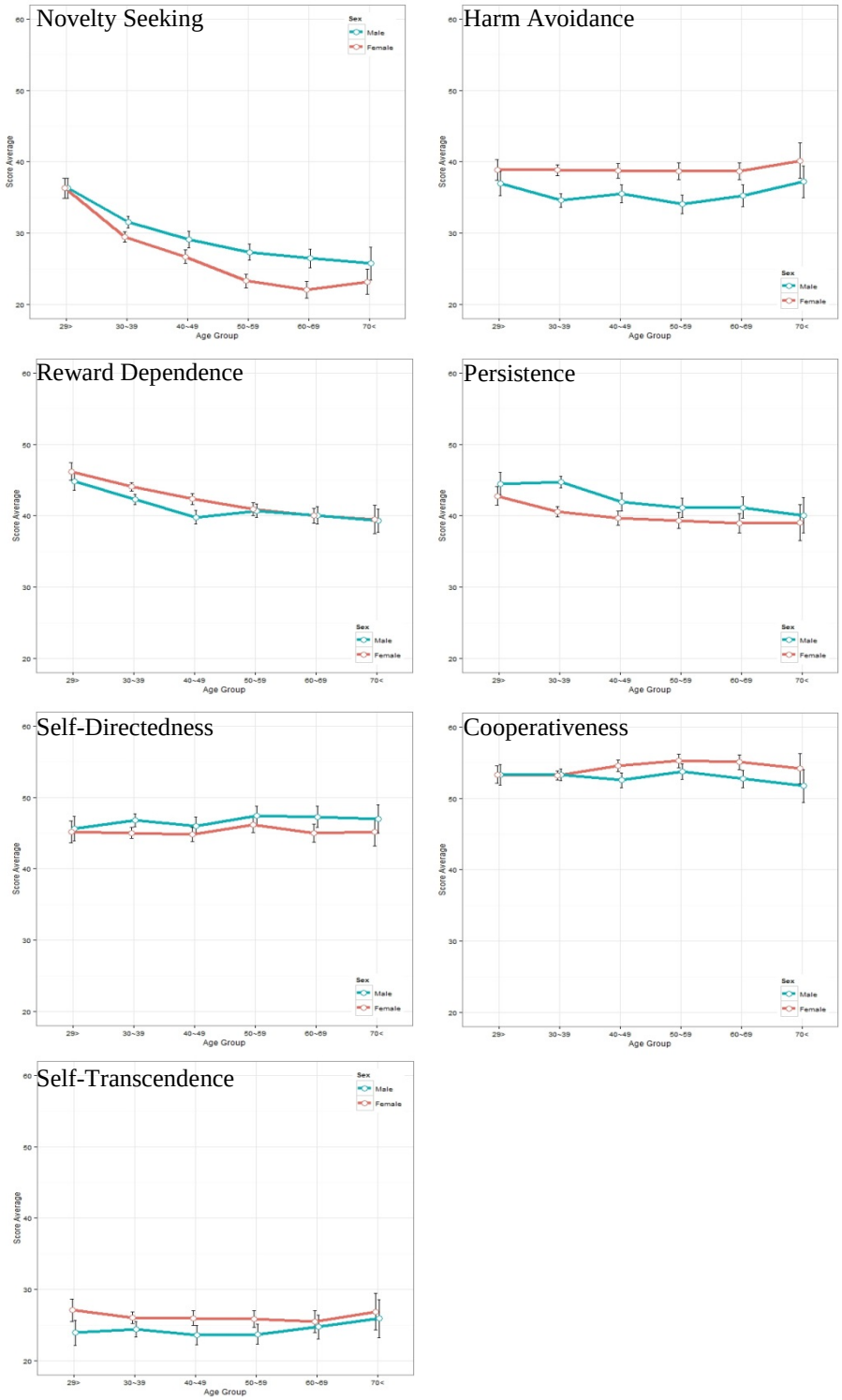


Table 2.3. Intraclass Correlations Coefficient (ICC) for Temperament and Character Inventory

	MZ Twin pairs (552pairs)	DZ Twin pairs (119 pairs)	DZ+SIB pairs (2856pairs)	P-O (2908 pairs)	Spouse (430 pairs)
Temperament					
NS	0.36	0.27	0.12	0.10	0.04
HA	0.43	0.00	0.14	0.10	0.10
RD	0.38	0.24	0.11	0.12	0.02
PE	0.42	0.14	0.14	0.08	0.06
Character					
SD	0.41	0.12	0.13	0.13	0.27
CO	0.39	0.11	0.15	0.13	0.20
ST	0.45	0.24	0.24	0.27	0.38

Abbreviations: NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence; MZ, Monozygotic; DZ, Dizygotic; SIB, sibling; P-O, Parent-offspring;
All rounded to the nearest tenth

Table 2.4. Dissection of Spouse's ICC by length of marriage

	Length of Marriage (Average Duration : 32 years)		
	≤30 years (95%CI) (176 pairs)	>30 years (95%CI) (256 pairs)	P value[a]
Temperament			
NS	0.03(-0.12-0.17)	0.05(-0.07-0.18)	0.77
HA	0.00(-0.15-0.15)	0.20(0.08-0.32)	0.004
RD	0.01(-0.14-0.16)	0.02(-0.10-0.15)	0.89
PE	0.05(-0.10-0.19)	0.08(-0.04-0.20)	0.66
Character			
SD	0.19(0.05-0.33)	0.33(0.21-0.43)	0.03
CO	0.15(0.00-0.29)	0.23(0.11-0.35)	0.23
ST	0.31(0.17-0.44)	0.42(0.31-0.52)	0.07

[a] obtained by Fisher's Z transformation

Abbreviations: CI, confidence interval; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence;

All rounded to the nearest tenth

Table 2.5. Correlation coefficients between various Δ between spouses and/or MZ and marriage duration (ΔSP and ΔMZ/ΔSP) or age (ΔMZ)

	spouse Δ (Δ_{SP})	P value [a]	MZ Δ(Δ_{MZ})	P value [b]	Matched (Δ_{MZ}/Δ_{SP}[c])	P value [a]
	Correlation with marriage duration (429 pairs)		Correlation with age (552 pairs)		Correlation with marriage duration (84 MZ cotwin-spouse matched trios)	
Temperament						
NS Δ	0.01	0.89	0.04	0.35	0.06	0.60
HA Δ	**-0.16**	**0.001**	0.00	0.99	-0.19	0.08
RD Δ	0.01	0.79	0.06	0.20	-0.06	0.58
PS Δ	-0.01	0.89	0.07	0.10	-0.05	0.63
Character						
SD Δ	**-0.16**	**0.001**	0.06	0.15	**0.23**	**0.04**
CO Δ	-0.02	0.71	0.06	0.16	0.00	0.99
ST Δ	-0.05	0.32	0.00	0.93	-0.09	0.40

Abbreviations: NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence; Δ, difference between pairs;

All rounded to the nearest tenth

[a] Correlation with Marriage Duration, age and sex adjusted

[b] Correlation with Age of twins

[c] Logarithmic transformation of ratio of Δ between one's co-twin's to Δ with one's spouse's after adding a constant 10 (84 trios, to logarithmic base 2), positive means more relative resemblance toward spouse, while negative means more toward one's cotwin along the marriage duration.

Range of all spouse's marriage duration was 14-63 years, in average 32.56 years; range of 84 subgroup spouses' marriage duration was 14-35 years, with average of 24.08 years

Table 2.6. Heritability Estimates with different common environmental effect adjustments for Temperament and Character Inventory

	ACE Model			ADE/ACDE Model				
	A(95%CI)	C(95%CI)	AIC	A(95%CI)	C (95%CI)	D(95%CI)	AIC	Variance due to covariates
Household model								
Temperament								
NS	0.31(0.25-0.36)		18681.63	**0.24(0.16-0.32)**		**0.12(0.01-0.23)**	**18678.67**	0.15
HA	0.31(0.26-0.37)		19476.02	0.19(0.11-0.27)		0.23(0.13-0.33)	19458.08	0.03
RD	0.30(0.24-0.35)		17623.88	**0.21(0.13-0.29)**		**0.16(0.06-0.26)**	**17616.24**	0.05
PE	0.29(0.24-0.35)		19211.62	**0.15(0.07-0.22)**		**0.28(0.18-0.38)**	**19184.06**	0.04
Character								
SD	0.31(0.25-0.37)		19322.07	0.20(0.12-0.28)		0.21(0.11-0.31)	19307.00	0.01
CO	0.31(0.22-0.39)	0.00(-0.05-0.05)	18219.04	0.17(0.05-0.29)	0.03 (-0.02-0.09)	0.17(0.06-0.27)	18210.33	0.01
ST	0.23(0.14-0.32)	0.15(0.10-0.21)	19741.75	0.13(0.03-0.24)	0.18 (0.12-0.23)	0.13(0.04-0.23)	19735.67	0.01
Sibling effect model								
Temperament								
NS	0.31(0.25-0.36)		18681.63	0.24 (0.16-0.32)		0.12(0.01-0.23)	18678.67	0.15
HA	0.27(0.20-0.34)	0.05(0.00-0.11)	19473.34	0.19 (0.11-0.27)		0.23(0.13-0.33)	19458.08	0.03
RD	0.27(0.20-0.34)	0.03(-0.02-0.09)	17624.14	0.21 (0.13-0.29)		0.16(0.06-0.26)	17616.24	0.05

PE	0.22(0.15-0.29)	0.10(0.04-0.15)	19200.81	0.14 (0.06-0.22)	0.02(-0.05-0.09)	0.26(0.14-0.38)	19185.72	0.04
Character								
SD	0.27(0.20-0.34)	0.05(0.00-0.10)	19320.62	0.20 (0.12-0.28)		0.21(0.11-0.31)	19307.00	0.01
CO	0.25(0.18-0.32)	0.08(0.02-0.13)	18210.72	0.22 (0.14-0.30)	0.05(-0.02-0.11)	0.10(-0.02-0.22)	18210.24	0.01
ST	0.41(0.35-0.47)	0.03(-0.01-0.08)	19768.09	0.41 (0.35-0.47)	0.03(-0.01-0.08)		19768.09	0.01
Spouse effect model								
Temperament								
NS	0.31(0.25-0.37)	0.06(-0.04-0.15)	18682.36	0.25(0.16-0.33)	0.04(-0.06-0.14)	0.11(0.01-0.21)	18680.11	0.15
HA	0.33(0.27-0.39)	0.14(0.05-0.24)	19469.29	**0.20(0.11-0.28)**	**0.12(0.02-0.22)**	**0.22(0.12-0.32)**	**19454.61**	0.03
RD	0.30(0.24-0.36)	0.03(-0.06-0.12)	17625.45	0.21(0.13-0.29)	0.01(-0.09-0.10)	0.16(0.06-0.25)	17618.22	0.05
PE	0.30(0.24-0.36)	0.08(0.00-0.16)	19210.00	0.15(0.07-0.23)	0.05(-0.04-0.14)	0.27(0.19-0.36)	19184.71	0.04
Character								
SD	0.33(0.27-0.39)	0.29(0.20-0.37)	19286.75	**0.21(0.12-0.30)**	**0.28(0.19-0.36)**	**0.20(0.11-0.28)**	**19276.25**	0.01
CO	0.33(0.27-0.38)	0.21(0.13-0.30)	18197.82	**0.25(0.16-0.33)**	**0.20(0.11-0.29)**	**0.12(0.03-0.21)**	**18194.18**	0.01
ST	**0.44(0.39-0.49)**	**0.29(0.22-0.37)**	**19719.73**	0.44(0.39-0.49)	0.29(0.22-0.37)		19719.73	0.01

Abbreviations: A, additive genetic effect estimates; C, shared environment effect estimate; D, non-additive genetic effect estimate; CI, confidence interval; AIC, Akaike's Information Criterion; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence

Covariates used: age, sex, age^2, age*sex, and age^2*sex interactions

All rounded to the nearest tenth, Best fitting models are in bold

3. Discussion

The temperament and character traits were both heritable to about the same degree, confirming the earlier findings in Asian and Caucasian populations [34-37, 40]. This finding differs from Cloninger's original hypothesis based on earlier personality tests [20], but is consistent with all studies directly evaluating the heritability of TCI measures. Nonetheless, evidence that the distinction between temperament and character is meaningful despite the similar heritabilities observed, as do other findings that show a distinct trajectory for the development of temperament and character over the life course [12] and greater influence of parental care-giving and home environment on personality development [89]. In particular, the common environmental effects shared by specific family relationships (i.e. spouses) were more important for character traits than for temperament; all character domains showed a substantial influence of common environment in our best fitting model, whereas the only temperament with a significant effect of common environment was HA. Also the estimates of C component were much higher for character traits (0.20-0.29) than the estimate for HA (0.12). Furthermore, the nature of influences of assortative mating and common environment on personality is complex and requires careful consideration and replication.

There can be several different explanations for the similarity of personality between spouses including assortative marriage, convergence of personality due to effects of shared environment, attribution of dissimilar couples by divorce, and confounding effects of age-related variables [90].

Many studies about spousal similarity concluded that significant ICC between couples is due to assortative marriage because personality traits are usually considered as unalterable phenotypes [91, 92], and not many of them found a significant correlation between years of marriage and differences in personality [93, 94]. This may be less important in our subjects due to high percentage of arranged marriage. In a Belgian study, ICC between spouses did not show a large difference between temperament and character domains, and only ST became more similar as the relationship length increased [95]. In our study, a strong evidence of resemblance between spouses for character traits was found but not for temperament traits, which is somewhat consistent with the Cloninger's theory of temperament and character traits having different background in developing them.

Assortative mating might explain at least a part of spousal correlations for character domains, supported by positive ICC in shorter marriage group (Table 2.4). However, it is important to recognize that the spousal resemblance could not be explained by an initial assortative mating only. In particular, the resemblance of HA, SD became significantly stronger as the duration of marriage increased. Dissection of personality traits showed a substantial effect of environment shared by couples as well as additive genetic effects for HA and all three character traits. Combining these findings, the evidence that personality gradually changes with duration of cohabitation is suggestive for HA and SD, and this change might be also possible for ST with marginal significance for change in resemblance.

Also the differences between couples decreased significantly for HA

and SD as the marriage length increased. Even when compared with one's cotwin's differences, SD significantly showed more similarity with one's spouse than with one's MZ cotwin indicating evidence of convergence of the trait among married couples. If the assumption that environments regarding marriage did not change substantially during this period is made, the correlation between spousal resemblance and marriage duration, as well as the ICC differences according to marriage duration should reflect the level of convergence rather than the differences in the degree of assortative mating between groups.

It is noteworthy that in a 2009 report by the Korea Institute for Health and Social Affairs, 41.8% of married women stated that their marriage was arranged, which implies that the influences of assortative marriage is lower in our subjects than in western populations. The divorce rate for the age of those married in this study (avg. 58 years) is 1.5~1.7 per 1,000 couples per year between 2007~2012 in Korea, and this is also evidenced by the long duration of marriage of our study participants. Our study could analyze whether the length of successful marriage will have any influence on the degree of convergence in personality traits. The average marriage duration in our study was 32.56 years, ranging from 14~63 years. This long duration could have selected the study subjects for successfulness in their marriage. Even if all the divorces are assumed to arise from irreconcilability in personality, the increasing resemblance of SD between spouses with marriage duration exceeds the possible effects of selection resulting from divorce.

As mentioned above, there has been more arranged marriages in

Korea than Western countries. One of the key features of social homogamy is marriages within the similar socio-economic strata, whether the marriage is arranged or not. To see if the social status has any relationship to personality traits, the average scores of each dimension were compared between the groups with different monthly household income. The following graph shows slight trend, but with large 95% confidence intervals, in the mean scores of TCI by different income groups. However, all TCI traits, besides SD, did not show a significant trend when age and gender was adjusted. Although SD shows slight increase with income level, the variation explained by the SD score is very small (about 1%) and it is not likely that this can explain the spousal correlation.

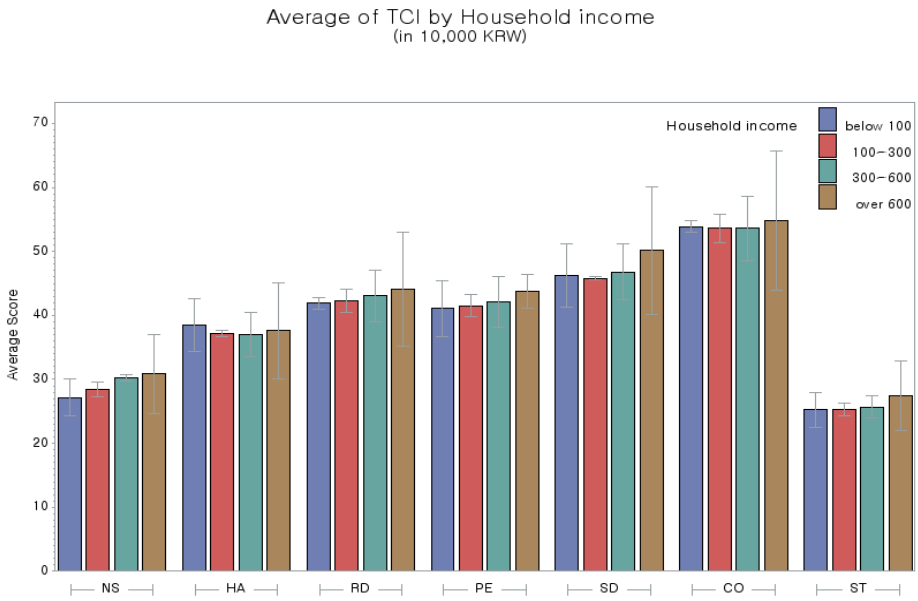


Figure 2.2. Average of TCI scores by monthly household income in 10,000 Korean Won (not accounted for sex or age)

Besides the population characteristics, the discrepancy with previous researches could have come from our study design which enabled us to analyze various family relationships, giving us strength in finding the evidence for convergence of personality and distinguishing whether it is influenced by genetic or environment factors. A Swedish study that also includes twins and their spouse samples reported that personality is an important factor for marriage satisfaction, which could be comparable with the duration of marriage in our study [96]. Moreover, our study could further analyze the influence of length of successful marriage on the degree of convergence in personality traits.

The common environmental effect of sharing household or being a partner had a dramatic effect on ST. Many families in Korea tend to have same religious beliefs. Also when both parents had the same religious beliefs, it had a strong effect on their children's religious behavior [97]. This finding illustrates the importance of social norm-favoring within a family for ST. On the other hand, there was substantial evidence for non-additive genetic effect for all traits of TCI except for ST. Because some of these complex genetic components exceeded the additive genetic component, the importance of non-additive genetic such as epistasis should be recognized in personality traits. Age showed a significant contribution to NS, and when age and sex were adjusted, there was no other shared environmental effect on variation in NS.

The cross-sectional nature of this study limits our ability to show that characters do change over the course of years. However, because the study subjects are representative of general population, and with low divorce rate of

the older age spouses in Korea, the most reasonable way of interpreting the positive trends between marriage duration and personality similarity, is the convergence over partnership duration. Also, very recent 10 year longitudinal study using Finnish cohort samples reported that population mean-level changes of character traits with age were very substantial, whereas temperament traits showed no change on average or only weak trends [12]. The Finnish findings are very consistent with our results, thus supporting our conclusions. For a note, HA showed near zero effect size in change over time in the Finnish study, whereas our study focused on convergence of personality due to shared environment. Moreover, by matching the MZ twins and spouses, whether the personality convergence is due to genetic or environment effects were distinguishable.

Our heritability analysis result suggests substantial amount of effect on HA from shared environment between spouses. However the effect was not as apparent as SD, and enough evidence was not present to conclude that the common environment has exceeding effect on HA than genes. Also our minimum duration of marriage was 12 years, which did not allow us to see the similarities between relatively newlywed couples and their contribution to our result. A covariate that could have been considered is a religious belief, especially on the ST dimension, but was unavailable.

This study demonstrates that there are genetic influences on not only temperament traits, but also on character traits. Our results support two important new findings: 1) the different domains of temperament and character do play distinct roles in shaping an individual's personality, and that

there are considerable influence of shared environmental effects on all character scales and HA, even though genetic influences are equally important for both domains, and 2) although spousal interactions have little influence on the development of partners' temperaments except HA, all human characters do appear to gradually change throughout the lifespan probably with varying degrees as a result of the influences of long-term close relationships. Particularly SD showed evidence of “more environmental” influences compared with age-dependent or genetic influences (cotwin comparisons) and conclusion that SD changes due to long-term shared environment was made, at least for those who are willing to change through partnership. In addition to this, the study distinguished differences between common environmental effects shared by siblings, spouses, and by all members of a household.

III. Genetic epidemiology of Personality

1. Material and Methods

1.1. Participants

Participants for this study are recruited with protocols which are same as the previous chapter. Please refer to Method section of Chapter 2 for more details.

1.2 Measurement of Personality – Five Factor Model

Additional personality assessment was performed using the Korean short version of the NEO PI-R (PSI Consulting Corp., Seoul, Korea), which has been tested for reliability and validity in Korean population [98]. This inventory is comprised of a 90-item questionnaire on a 5-point Liker-type scale to characterize the Five Factor Model (FFM). The five dimensions of the FFM are neuroticism, extraversion, openness, agreeableness, and conscientiousness. The scores of FFM were calculated as sum of 18 items per factors, with some negatively keyed items being reversed. The quality control of the FFM was conducted according to the NEO PI-R manual, and invalid or missing items were excluded. Total of 1,169 participants (476 male, 693 female) of the Healthy Twin Study with NEO PI-R scores, who also has measurement of TCI, were included in this study.

1.3. Genotype Data

Genomic DNA was extracted from the whole-blood samples obtained from the subjects participating in Healthy Twin Study. The study

sample's genotyping was performed on two different platforms; 1) Affymetrix Genome-Wide Human array 6.0 (Affymetrix, Inc. Santa Clara, CA, USA, n=2,260) and 2) Illumina Infinium Humancore Beadchips (Illumina, San Diego, CA, USA, n=1,194). Genotyped markers with duplicated SNPs, Hardy-Weinberg Equilibrium p-value < $1x10^{-6}$, Minor Allele frequency < 0.01, low call rate (< 90%) were quality controlled, resulting in 516,452 markers for Affymetrix genotype and 186,965 markers for Illumina platform. The data cleaning of the genotypes and development of input files for further analysis was performed using the PLINK software [99].

The markers were imputed using Asian population (n=286) of 1000 Genome haplotypes phase I integrated variant set release GRch37/hg19 (http://www.1000genomes.org/) as a reference panel. Pre-phasing of genotypes was performed using SHAPEIT (v2.r837) [100], and SNP imputation was performed using IMPUTE2 (2.3.2) [101]. After filtering for INFO score $\geq$ 0.9, and cross-checking for two different platforms, further quality control with same criteria above was completed resulting in 4,174,873 variants for genetic analysis.

1.4. Statistical analyses

1.4.1. Genome-wide association analysis

For the genome-wide association analysis, a family-based univariate association test using mixed-effect variance component approach of family-based association test [102] implemented in the Merlin (multipoint engine for

rapid likelihood inference) [103] package was performed for each personality dimensions.

Basic model for the association is the linear model, where the genetic effects are considered as additive for each SNP, and defining the linear model testing for association between phenotype in interest and genotype is as follow.

$$\mathrm{E}(Y_{ij}) = \mu + \beta_g g_{ij} + \beta_x X_{ij}$$

In the equation above, Y is defined as the phenotype, μ as the population mean, g as additive genetic score, X as covariate, β_g as estimated additive genetic effect for each SNP, and β_x as estimated covariate effects. The associations of the genotype and personality traits were confirmed with the level of significance of β_g.

To account for the correlation between related individuals from a family, a variance-covariance matrix Ω_{ijk} for individual *j* and *k* in *i*-th family is considered in the model. Ω_{ijk} is defined as follow.

$$\Omega_{ijk} = \begin{cases} \sigma_a^2 + \sigma_g^2 + \sigma_e^2 & if\ j = k \\ \pi_{ijk}\sigma_a^2 + 2\varphi_{ijk}\sigma_g^2 & if\ j \neq k \end{cases}$$

In the equation above, σ_g^2 denotes major genetic effect, which is a kinship matrix at a marker, shared when individuals are identical by decent (IBD). σ_a^2 represents additive polygenic component, whereas σ_e^2 is non-shared environmental effect using the identity matrix. The π_{ijk} is estimated using the number of alleles shared IBD at the SNP being tested between individual *j*

and *k*, and φ_{ijk} is the theoretical kinship coefficient for these two individuals.

The family based association tests have several advantages. They are robust to population stratification, and because related individuals share a large fraction of their genotypes, it can be used to increase the power of the study [102] by imputing the unobserved genotype. Among the several approaches of testing the association between a genotype and phenotype in interest, a score test method [102], which is computationally less demanding than maximum-likelihood with minimal loss of power, was used. Following is the score statistics.

$$T^{score} = \frac{\left\{\sum_i [\bar{g}_i - E(\bar{g}_i)]' \left[\Omega_i^{(base)}\right]^{-1} [y_i - E(y_i)^{(base)}]\right\}^2}{\sum_i [\bar{g}_i - E(\bar{g}_i)]' \left[\Omega_i^{(base)}\right]^{-1} [\bar{g}_i - E(\bar{g}_i)]}$$

In the statistics, $E(y_i)^{(base)}$ represents a vector of fitted values for each *i*-th family, $\Omega_i^{(base)}$ is the estimated variance-covariance matrix, $\bar{g}_i$ denotes a vector of expected genotype scores for each individual, and $E(\bar{g}_i)$ is a vector of identical elements that allows the unconditional expectation of each genotype score. $T^{score}$is approximately chi-squared distributed with 1 degree of freedom. Score test requires only single numerical optimization for estimation of $\Omega_i^{(base)}$ and $E(y_i)^{(base)}$, which allows computational efficiency of this tool.

Age and sex was used as covariates for each personality traits. In order to account for the multiple comparisons, false discovery rate (FDR) was

applied. Annotation and information of the top 20 SNPs of each trait were obtained from Ensembl website (http://www.ensembl.org/) [104] and from NCBI database (http://www.ncbi.nlm.nih.gov/).

1.4.2. Visualization

Using the genome-wide association results, several methods were used to visualize the analysis results. First, quantile-quantile (Q-Q) plots and Manhattan plots were plotted using 'qqman' package [105] implemented in R package (v 3.2.3 http://www.R-project.org/). Q-Q plot compares the observed p-value versus the expected p-value from the null distribution of hypothesis of no association, allowing the researchers to display the relevance of association, and check for systematic bias or population stratification at a glance. The genomic inflation factor λ_{gc} was also calculated by dividing the median of the observed chi-squared test statistics by expected median of chi-squared distribution. Manhattan plots the $-\log_{10}$ of p-value from the association analyses on the Y-axis, and genomic coordinates on X-axis, visualizing the genomic loci with strong association. Using Locus Zoom [106], regional plots of the genome-wide significant loci with information of local linkage disequilibrium and recombination patterns were generated using 1000 Genomes JPT+CHB as a reference. The analysis of linkage disequilibrium (LD) among the region in interest was plotted using Haploview version 4.2 (www.broad.mit.edu/mpg/haploview).

1.4.3. Multivariable genome-wide association analysis

Because many studies using univariate analysis approach was not successful in finding the genetic loci with strong association with most of the personality traits despite their moderate heritabilities, a relatively novel approach, which is multivariate analysis using two different taxonomies of TCI and FFM was performed. Theoretically, the factors in each inventory are orthogonal [30, 107, 108], so multivariate analysis using different personality traits from independent models might give us some insights into the genetic background of personality.

Multivariate analysis, which is a joint analysis of multiple correlated traits have several advantages over univariate analysis. One is that due to extra information from the cross-trait covariance, multivariate analysis can have an increased power when there are genetic correlations between the traits [109]. Also because researcher can reduce the number of performed test, alleviating the burden for multiple testing is possible [110], and the results can be more consistent with biology when a pleiotropy is present among different traits [111, 112].

The multiple family-based quasi-likelihood score test (MFQLS) [113] ,that considers correlated variables and can be applied to family-based study, was used for multivariate analysis of TCI and FFM. The linear mixed model is used for the disease model, and X is defined as matrix of sample size (N) and variants (M), Y as N × phenotype (Q) matrix, Z as covariate column vector, B as vector of random effect for an additive polygenic effect

accounting for kinship coefficient matrix Φ with kinship coefficient π, E as a random error. ⊗ indicates the Kronecker product, which is a type of an operation on two matrices. Also, let 1_w be $1 \times w$ column vector and I_w as the $w \times w$ identity matrix. The following is the linear mixed model used for phenotypes in interest.

$$Y^q = Z\alpha_q + \sum_{m=1}^{M} X^m \beta_{mq} + B^q + E^q, \qquad \text{vec(B)} = \sim MVN(0, \Phi \otimes \sum \text{B})$$

The null hypothesis of this test is that for all β_{MQ}, the effect of variant m on phenotype q equals to 0, and the alternative hypothesis is H_0 being false. The test is conducted by comparing the genotype frequencies according to different phenotypes. The quasi-likelihood score function is applied to estimate the association between the genotype and multiple phenotypes. Instead of assuming a probability model for the data, quasi-likelihood allows one to only specify a relationship between the mean and variance when fitting a model. Working correlation matrix for X (V) and offset μ, introduced to adjust for phenotypes, are incorporated in the test statistics to maximize the efficiency. If $\text{var}(X_{ij}) = 2\pi_{ij,i'j'}\Psi$ is assumed, $\text{var}(vec(X)) = \Psi \otimes \Phi$ is also assumed and Ψ can be estimated with a sample variance covariance matrix. The quasi maximum likelihood estimate of minor allele frequencies of a genetic variant p can be calculated by

$$\hat{\text{p}} = \{(1_N^t \Phi^{-1} 1_N)^{-1} 1_N^t \Phi^{-1} X\}^t$$

And following assumption is further made.

$$\mathrm{vec}(\mathrm{X}) = (I_m \otimes 1_N)\mathrm{p}, \quad \mathrm{var}(\mathrm{vec}(\mathrm{x})) = \Psi \otimes \Phi$$

For family-based multivariate association test, following denotation is made.

$$\mathrm{A} = \Phi^{-1} - \Phi^{-1}1_N(1_N^t\Phi^{-1}1_N)^{-1}1_N^t\Phi^{-1}$$

Following is the statistics for MFQLS, where T=Y- μ. Won et al. (2015) suggested that the best efficient choice for V in quasi-likelihood score is the identity matrix, and μ is the best linear unbiased predictor (BLUP) from the linear mixed model.

$$\mathrm{S} = \mathrm{vec}(\mathrm{T}^t\Phi\mathrm{AX})$$

$$\mathrm{var}\,(\mathrm{S}) = \sum_{i,j,i',j'} \mathrm{cov}\left(\mathrm{S}_{ij}, \mathrm{S}_{i'j'}\right) = \Psi \otimes (\mathrm{T}^t\Phi\mathrm{A}\Phi\mathrm{T})$$

$$\mathrm{S}^t\mathrm{var}(\mathrm{S})^{-1}\mathrm{S} \sim \chi^2\,(df = MQ) \text{ under } H_0$$

Age and sex was included in the model as covariates. Total of 973 individuals with both TCI and FFM scores available was used for this analysis, and only one individual of each monozygotic twin pairs was randomly selected. Correlation between TCI traits and FFM traits were calculated using the SAS software (SAS Institute, Cary NC) with the residuals adjusted for age and gender. Multivariate heritability analysis was performed using SOLAR (Texas Biomedical Research Institute), accounting for family relationships, and environmental and genetic correlation between the TCI and FFM traits were estimated.

1.4.4. Replication with previously reported studies

List of SNPs that were reported to have borderline significance, or genome-wide significant association with personality traits from previously published studies were compared to the results of the present study. The details of the each published GWA studies are summarized in sTable 1.

1.4.5. Pathway Analysis

For the personality traits that showed genome-wide significant variants, a pathway analysis was performed. All SNPs with P <0.0001 in those traits were examined to see whether they are a part of known biological pathways, using the Ingenuity Pathway Analysis program (IPA, Ingenuity Systems, CA, USA). The likelihood of finding the association more than a random chance is calculated using the Fisher's exact test, and Benjamini-Hochberg method [114] implemented in IPA was applied for multiple testing correction for p-values,

1.4.6. Phenotypic variance explained by all available SNPs

GCTA software [115, 116] was used to estimate the proportion of variance in personality explained by additive effect of available or common SNPs. The genetic relationship matrix (GRM) was estimated between pairs of individuals from the SNPs, and restricted maximum likelihood analysis was performed. The ratio of genetic variance to phenotypic variance was interpreted as the SNP-based heritability. Sex and age was adjusted for this analysis, and the matrix of pedigree structure was additionally fitted to avoid confounding from shared environment.

1.4.7. Winner's curse adjustment for Univariate GWAS results

Winner's curse is a bias on the effect size that is occurred commonly in genome-wide association studies where the researcher's focus is mainly on the variants that has very low p-values or genome-wide significant, and these effects size estimates tend to be overestimated. To adjust for this bias, FDR Inverse Quantile Transformation method (FIQT) [117] was used for the effect size estimates from univariate association analysis. This method uses false discovery rate to adjust for multiple comparison, and uses the adjusted p-value to back transform the Z-score to normal quantile for estimation of adjusted beta estimates, with the same sign of the original statistics.

2. Results

2.1. Univariate Genome-wide association analysis for TCI

Total of 3,428 subjects with TCI measures were included in the univariate genome-wide association analysis. Because monozygotic twins share identical genetic characteristics, only one of the twins was genotyped, and the genotype was replicated for the cotwin. The top 20 ranked genome-wide association results and statistics are displayed in Table 3.1.

Among the seven dimensions of TCI, only cooperativeness (CO), which is a trait of character, had the genome-wide significant p-value of

9.05E-08 for rs56197244. This SNP is an intron of *ADAMTS17* (ADAM metallopeptidase with thrombospondin type 1 motif 17) gene located in chromosome 15, that encodes ADAMTS protein family with no known function determined yet (information obtained from NCBI database). After multiple testing correction of FDR, the SNPs associated with *ADAMTS17* were still significant at the alpha-level of 0.05, and the region explained about 1.21% of CO's variance (Table 3.2). The inflation factors for all TCI dimensions were acceptable to indicate the minimal inflation of test statistics ($\lambda_{gc} =$ 1.01-1.04). Manhattan plots and Q-Q plots for all seven TCI dimensions are displayed in Figure 3.1, 3.2, and 3.3. Regional plot of rs56197244 showed that other SNPs located closely with significant p-values were in high linkage disequilibrium (LD, r^2 >0.8) (Figure 3.4).

When CO's effect sizes were adjusted for the winner's curse, the original beta of rs5619724, 1.928 was decreased to 0.831 by using the FDR adjusted p-values. Effect size for rs74037521 (1.954) was adjusted to 0.842, and other SNPs with significant p-values within *ADAMTS17* with beta size above 1.9 were all adjusted to be about 0.83~0.84. The variance explained by single SNP of rs5619724 was 0.017 before winner's curse adjustment, but decreased to 0.003 after the adjustment, indicating substantial bias caused by the winner's curse.

Table 3.1. Top 20 ranked SNPs associated with each Temperament and Character Inventory dimensions

Abbreviations: Chr, Chromosome; SNP, single nucleotide polymorphism; MAF, Minor allele frequency; SE, Standard Error; Alleles – Major Allele/Minor Allele
All rounded to the nearest tenth

Novelty Seeking

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
5	rs16875692	G/A		Intergenic	0.12	-2.11	0.44	2.04E-06
5	rs3894130	G/A		Intergenic	0.12	-2.11	0.44	2.04E-06
14	rs61977989	G/A	PRKD1	Intron	0.18	-1.81	0.39	2.59E-06
14	rs61977991	C/T	PRKD1	Intron	0.18	-1.80	0.38	2.74E-06
15	rs138699947	G/T	DAPK2	Intron	0.08	-2.52	0.54	3.11E-06
15	rs75562796	T/C	DAPK2	Intron	0.08	-2.52	0.54	3.11E-06
15	rs76114015	A/G	DAPK2	Intron	0.08	-2.52	0.54	3.11E-06
15	rs76604991	C/G	DAPK2	Intron	0.08	-2.52	0.54	3.11E-06
15	rs11637916	G/A	DAPK2	Intron	0.08	-2.50	0.54	4.11E-06
15	rs184556	C/G	DAPK2	Intron	0.12	-2.10	0.46	5.60E-06
15	rs332280	T/C	DAPK2	Intron	0.12	-2.10	0.46	5.60E-06
15	rs332286	G/C	DAPK2	Intron	0.12	-2.10	0.46	5.60E-06
15	rs74021232	A/G	DAPK2	Intron	0.12	-2.10	0.46	5.60E-06
15	rs74021233	A/G	DAPK2	Intron	0.12	-2.10	0.46	5.60E-06
15	rs78221970	A/C	DAPK2	Intron	0.12	-2.10	0.46	5.60E-06
15	rs4776282	G/T	DAPK2	Intron	0.12	-2.11	0.46	5.76E-06
14	rs4981054	T/C	PRKD1	Intron	0.18	-1.73	0.38	5.77E-06
15	rs332278	G/C	DAPK2	Intron	0.12	-2.09	0.46	6.43E-06
11	rs12574868	A/G	RPL34P23	Downstream	0.09	2.21	0.49	6.80E-06
4	rs79366726	C/T		Intergenic	0.07	2.43	0.54	7.04E-06

Harm Avoidance

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
11	rs11215419	A/T	CADM1	Intron	0.15	2.24	0.45	6.73E-07
11	rs9645660	C/T	CADM1	Intron	0.15	2.23	0.45	6.82E-07
18	rs623744	A/G		Intergenic	0.29	-1.81	0.39	2.49E-06
12	rs12812781	C/T		Intergenic	0.04	4.21	0.92	4.79E-06
12	rs34618998	T/C		Intergenic	0.04	4.09	0.91	7.92E-06
18	rs78070578	T/A		Intergenic	0.28	-1.75	0.39	7.94E-06
18	rs1600925	C/G		Intergenic	0.28	-1.74	0.39	8.57E-06
18	rs9319757	T/C		Intergenic	0.28	-1.74	0.39	8.77E-06
18	rs9319758	T/G		Intergenic	0.28	-1.74	0.39	8.77E-06
18	rs9958506	T/G		Intergenic	0.28	-1.74	0.39	8.77E-06
2	rs59099299	T/C	CCDC150	Intron	0.04	3.87	0.87	8.84E-06
2	rs12470005	C/G	CCDC150	Intron	0.04	3.87	0.87	8.86E-06

20	rs1512061	A/G		Intergenic	0.06	3.25	0.73	9.50E-06
12	rs57688645	G/A		Intergenic	0.04	4.00	0.91	9.94E-06
18	rs9962976	C/T		Intergenic	0.28	-1.72	0.39	1.04E-05
18	rs1943056	G/C		Intergenic	0.28	-1.72	0.39	1.04E-05
18	rs565621	G/A		Intergenic	0.45	-1.50	0.34	1.06E-05
2	rs150853794	A/G	CCDC150	Intron	0.05	3.57	0.81	1.08E-05
20	rs28434366	A/G		Intergenic	0.06	3.23	0.74	1.11E-05
11	rs2053000	A/T		Intergenic	0.46	1.43	0.33	1.18E-05

Reward Dependency

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
12	rs117633021	C/T	SOCS2-AS1	Intron	0.12	2.25	0.45	5.17E-07
12	rs11614062	A/T	SOCS2-AS1	Intron	0.12	2.24	0.45	5.19E-07
2	rs144511775	G/A	RNU5E-9P	Downstream	0.01	7.03	1.44	1.03E-06
14	rs2416187	C/A		Intergenic	0.43	1.33	0.28	2.69E-06
18	rs146591879	C/T	DYM	Intron	0.39	1.40	0.30	2.72E-06
17	rs185099440	T/C	COG1	Intron	0.02	-5.03	1.08	3.03E-06
18	rs8087711	T/A	DYM	Intron	0.39	1.40	0.30	3.13E-06
18	rs62102349	G/A	DYM	Intron	0.39	1.39	0.30	3.27E-06
18	rs11665239	G/A	DYM	Intron	0.39	1.39	0.30	3.33E-06
3	rs74849663	A/G	CACNA2D3	Intron	0.08	2.20	0.48	3.83E-06
3	rs4077645	T/C	CACNA2D3	Intron	0.08	2.19	0.48	4.14E-06
12	rs11061946	C/T	ADIPOR2	Intron	0.36	-1.32	0.29	4.43E-06
18	rs8092381	T/C	DYM	Intron	0.40	1.36	0.30	4.75E-06
12	rs11061952	G/A	ADIPOR2	Intron	0.36	-1.32	0.29	5.03E-06
12	rs73040715	C/T	ADIPOR2	Intron	0.36	-1.32	0.29	5.12E-06
2	rs12617950	A/C	GALNT13	Intron	0.44	-1.27	0.28	5.21E-06
18	rs7237062	T/C	DYM	Intron	0.40	1.35	0.30	5.44E-06
2	rs6435170	C/A	GALNT13	Intron	0.44	-1.27	0.28	5.67E-06
12	rs73040736	C/T	ADIPOR2	Intron	0.36	-1.31	0.29	6.11E-06
2	rs6726767	T/A	GALNT13	Intron	0.44	-1.27	0.28	6.28E-06

Persistence

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
10	rs60832004	T/A	SNRPGP6	Upstream	0.12	2.32	0.48	1.21E-06
10	rs73377406	C/A	SNRPGP6	Upstream	0.12	2.32	0.48	1.21E-06
10	rs73375802	G/A		Intergenic	0.12	2.32	0.48	1.23E-06
10	rs59729475	A/G		Intergenic	0.12	2.32	0.48	1.23E-06
10	rs11816076	G/A		Intergenic	0.12	2.32	0.48	1.23E-06
10	rs1835666	C/G	SNRPGP6	Upstream	0.12	2.30	0.48	1.44E-06
1	rs17129381	A/T	SGIP1	Intron	0.44	1.52	0.32	2.32E-06
8	rs7012161	C/T	RP11-705O24.1	Intron	0.32	-1.61	0.34	2.52E-06

8	rs35929132	T/C	RP11-705O24.1	Intron	0.32	-1.58	0.34	3.32E-06
10	rs114940146	C/T		Intergenic	0.11	2.33	0.50	3.52E-06
1	rs1325267	C/T	SGIP1	Intron	0.45	1.47	0.32	3.84E-06
1	rs12728269	G/A	SGIP1	Intron	0.45	1.47	0.32	4.21E-06
8	rs13254880	T/C	RP11-705O24.1	Intron	0.32	-1.56	0.34	4.50E-06
5	rs286969	G/A		Intergenic	0.11	2.28	0.50	4.76E-06
1	rs12565436	C/T	SGIP1	Intron	0.45	1.45	0.32	5.10E-06
1	rs17129332	C/G	SGIP1	Intron	0.45	1.45	0.32	5.10E-06
1	rs9633417	C/A	SGIP1	Intron	0.45	1.45	0.32	5.12E-06
1	rs34868698	T/G	SGIP1	Intron	0.45	1.45	0.32	5.45E-06
1	rs1853772	A/G	SGIP1	Intron	0.45	1.44	0.32	5.60E-06
1	rs12035546	C/T	SGIP1	Intron	0.45	1.44	0.32	5.87E-06

Self-Directedness

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
22	rs461869	G/C		Intergenic	0.30	1.64	0.35	3.742E-06
5	rs7707957	A/G		Intergenic	0.11	-2.30	0.50	4.075E-06
5	rs6596610	T/G		Intergenic	0.11	-2.30	0.50	4.087E-06
5	rs4392597	G/T		Intergenic	0.11	-2.30	0.50	4.088E-06
5	rs4392598	G/C		Intergenic	0.11	-2.30	0.50	4.088E-06
5	rs4989762	C/A		Intergenic	0.11	-2.30	0.50	4.089E-06
5	rs10455067	A/G		Intergenic	0.11	-2.30	0.50	4.09E-06
5	rs7702850	T/C		Intergenic	0.11	-2.30	0.50	4.09E-06
5	rs7715902	G/T		Intergenic	0.11	-2.30	0.50	4.09E-06
5	rs7708571	A/G		Intergenic	0.11	-2.30	0.50	4.091E-06
5	rs7725736	G/T		Intergenic	0.11	-2.30	0.50	4.091E-06
5	rs7700776	T/C		Intergenic	0.11	-2.30	0.50	4.28E-06
5	rs7722250	T/C		Intergenic	0.11	-2.29	0.50	4.402E-06
5	rs7725955	T/C		Intergenic	0.11	-2.31	0.50	4.561E-06
5	rs4392596	T/C		Intergenic	0.11	-2.30	0.50	4.715E-06
22	rs463271	C/T	FLJ41941	Downstream	0.30	1.61	0.35	5.331E-06
4	rs360938	T/C	RP11-73G16.2	Intron	0.11	2.54	0.56	5.391E-06
5	rs140114078	G/T		Intergenic	0.15	2.07	0.46	5.566E-06
3	rs6762831	A/G	MAGI1	Intron	0.05	-3.27	0.72	6.047E-06
5	rs2609671	G/A		Intergenic	0.15	2.06	0.46	6.171E-06

Cooperativeness

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
15	rs56197244	T/C	ADAMTS17	Intron	0.24	1.93	0.36	9.05E-08

15	rs74037521	A/G	ADAMTS17	Intron	0.23	1.95	0.37	9.22E-08
15	rs78233554	G/T	ADAMTS17	Intron	0.23	1.95	0.37	9.25E-08
15	rs74037531	A/C	ADAMTS17	Intron	0.24	1.92	0.36	9.69E-08
15	rs77107779	T/C	ADAMTS17	Intron	0.23	1.96	0.37	9.87E-08
15	rs76152247	T/A	ADAMTS17	Intron	0.24	1.92	0.36	1.21E-07
15	rs74037542	T/C	ADAMTS17	Intron	0.24	1.90	0.36	1.32E-07
15	rs74581283	A/G	ADAMTS17	Intron	0.24	1.90	0.36	1.32E-07
15	rs57623076	A/G	ADAMTS17	Intron	0.24	1.90	0.36	1.32E-07
15	rs74037545	A/T	ADAMTS17	Intron	0.24	1.90	0.36	1.32E-07
15	rs57558908	C/G	ADAMTS17	Intron	0.24	1.90	0.36	1.32E-07
15	rs59562882	G/T	ADAMTS17	Intron	0.24	1.90	0.36	1.32E-07
15	rs58875131	G/A	ADAMTS17	Intron	0.24	1.90	0.36	1.32E-07
15	rs55998414	G/C	ADAMTS17	Intron	0.24	1.90	0.36	1.33E-07
15	rs57163390	C/T	ADAMTS17	Intron	0.24	1.90	0.36	1.33E-07
15	rs61249758	G/A	ADAMTS17	Intron	0.24	1.90	0.36	1.33E-07
15	rs74037539	G/A	ADAMTS17	Intron	0.24	1.90	0.36	1.33E-07
15	rs74037540	T/C	ADAMTS17	Intron	0.24	1.90	0.36	1.33E-07
15	rs4594243	C/T	ADAMTS17	Intron	0.24	1.90	0.36	1.33E-07
15	rs4627320	A/G	ADAMTS17	Intron	0.24	1.90	0.36	1.33E-07

Self-Transcendence

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
3	rs4908946	T/A	TBC1D5	Intron	0.04	-4.44	0.95	2.86E-06
3	rs4908947	C/A	TBC1D5	Intron	0.04	-4.44	0.95	2.86E-06
6	rs11968273	C/G		Intergenic	0.48	-1.56	0.34	5.14E-06
6	rs4896278	C/T		Intergenic	0.48	-1.56	0.34	5.14E-06
6	rs203695	T/C	BTF3L4P3	Downstream	0.46	-1.49	0.34	1.29E-05
10	rs72819857	A/G	LCOR	Intron	0.24	1.77	0.41	1.68E-05
10	rs7895214	G/T	LCOR	Intron	0.25	1.74	0.41	1.74E-05
4	rs998719	C/T	SLC39A8	Intron	0.12	2.26	0.53	1.76E-05
9	rs616040	G/T	PTPRD	Intron	0.37	-1.58	0.37	1.77E-05
8	rs7828867	A/G	ZFAT	Intron	0.25	-1.70	0.40	1.93E-05
14	rs1884235	A/C	NOVA1-AS1	Intron	0.28	1.65	0.39	2.04E-05
4	rs72692261	G/A	SLC39A8	Intron	0.12	2.24	0.53	2.19E-05
4	rs11724124	A/G	SLC39A8	Intron	0.12	2.23	0.53	2.21E-05
4	rs11735688	T/C	SLC39A8	Intron	0.12	2.23	0.53	2.21E-05
4	rs4699013	C/T	SLC39A8	Intron	0.12	2.23	0.53	2.27E-05
15	rs7177499	G/T	ADAMTS17	Intron	0.40	1.47	0.35	2.33E-05
3	rs6442690	T/G		Intergenic	0.33	-1.58	0.37	2.52E-05

16	rs1922618	G/T	WWOX	Intron	0.09	2.47	0.59	2.76E-05
9	rs694201	C/A	PTPRD	Intron	0.36	-1.53	0.37	2.90E-05
6	rs72830758	A/T	LRRC16A	Intron	0.34	-1.55	0.37	2.99E-05

Table 3.2. P-values after multiple comparisons and heritability explained by each variant for Cooperativeness

Chr	SNP	Gene	P-value	FDR	BonF	H2
15	rs56197244	ADAMTS17	9.05E-08	0.02	0.38	1.21
15	rs74037521	ADAMTS17	9.22E-08	0.02	0.39	1.23
15	rs78233554	ADAMTS17	9.25E-08	0.02	0.39	1.23
15	rs74037531	ADAMTS17	9.69E-08	0.02	0.40	1.21
15	rs77107779	ADAMTS17	9.87E-08	0.02	0.41	1.23
15	rs76152247	ADAMTS17	1.21E-07	0.02	0.51	1.19
15	rs74037542	ADAMTS17	1.32E-07	0.02	0.55	1.18
15	rs74581283	ADAMTS17	1.32E-07	0.02	0.55	1.18
15	rs57623076	ADAMTS17	1.32E-07	0.02	0.55	1.18
15	rs74037545	ADAMTS17	1.32E-07	0.02	0.55	1.18
15	rs57558908	ADAMTS17	1.32E-07	0.02	0.55	1.18
15	rs59562882	ADAMTS17	1.32E-07	0.02	0.55	1.18
15	rs58875131	ADAMTS17	1.32E-07	0.02	0.55	1.18
15	rs55998414	ADAMTS17	1.33E-07	0.02	0.55	1.18
15	rs57163390	ADAMTS17	1.33E-07	0.02	0.55	1.18
15	rs61249758	ADAMTS17	1.33E-07	0.02	0.55	1.18
15	rs74037539	ADAMTS17	1.33E-07	0.02	0.55	1.18
15	rs74037540	ADAMTS17	1.33E-07	0.02	0.55	1.18
15	rs4594243	ADAMTS17	1.33E-07	0.02	0.56	1.18
15	rs4627320	ADAMTS17	1.33E-07	0.02	0.56	1.18

Abbreviations: Chr, Chromosome; SNP, single nucleotide polymorphism; FDR, False Discovery Rate; BonF, Bonferroni correction; H2, the variation of phenotype explained by the SNP;

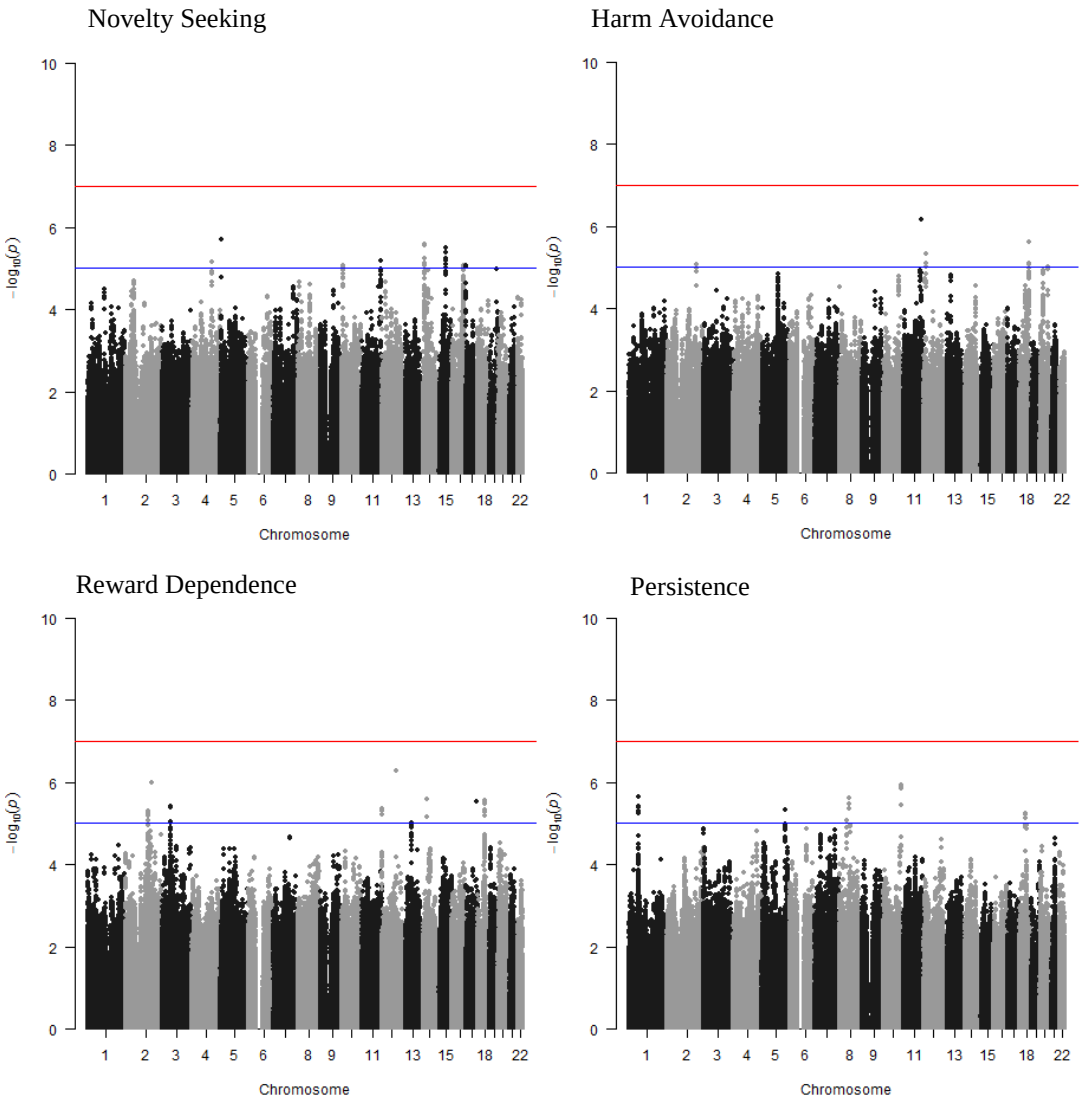


Figure 3.1. Manhattan plot for the association result of Temperament traits of Temperament and Character Inventory (TCI)

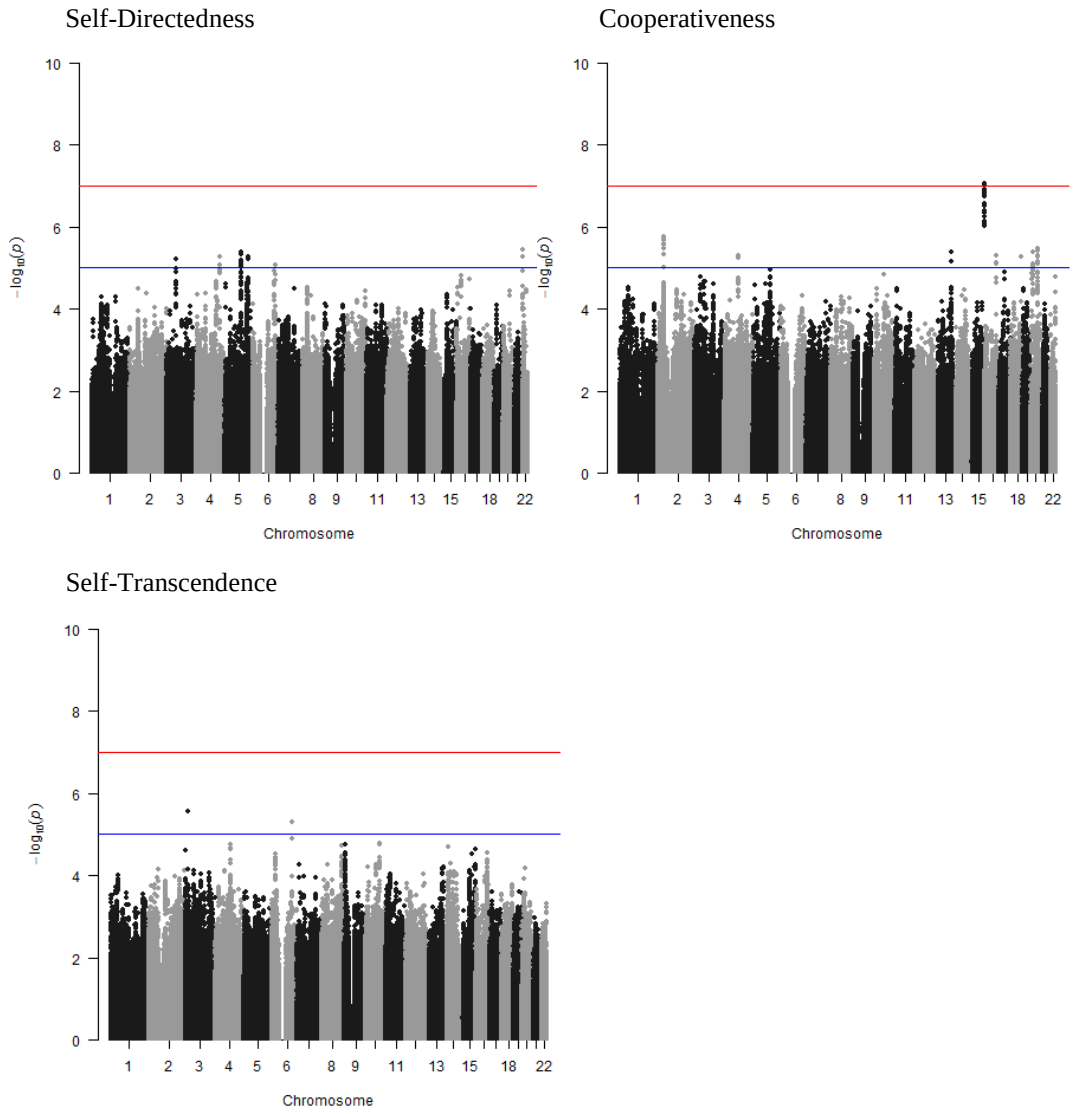


Figure 3.2. Manhattan plot for the association result of Character traits of Temperament and Character Inventory (TCI)

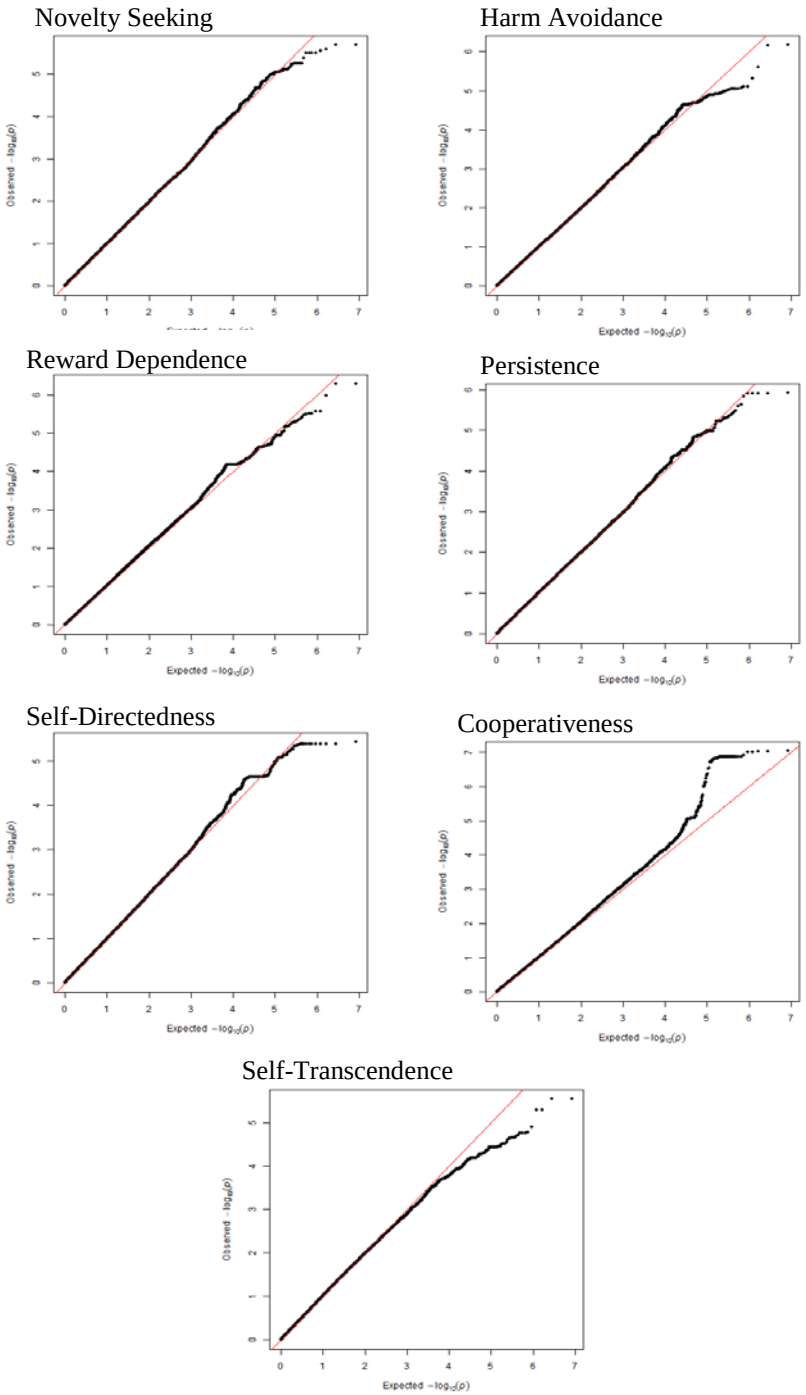
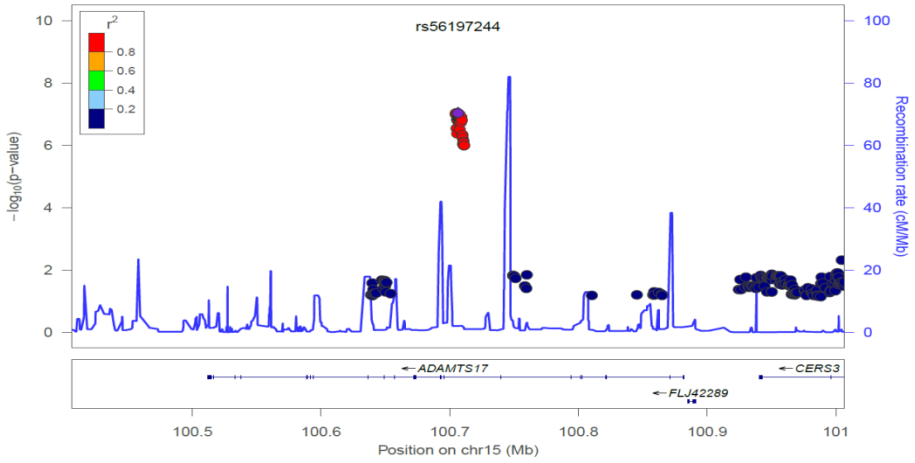


Figure 3.3. Q-Q plot for the association result of Temperament and Character Inventory (TCI) traits



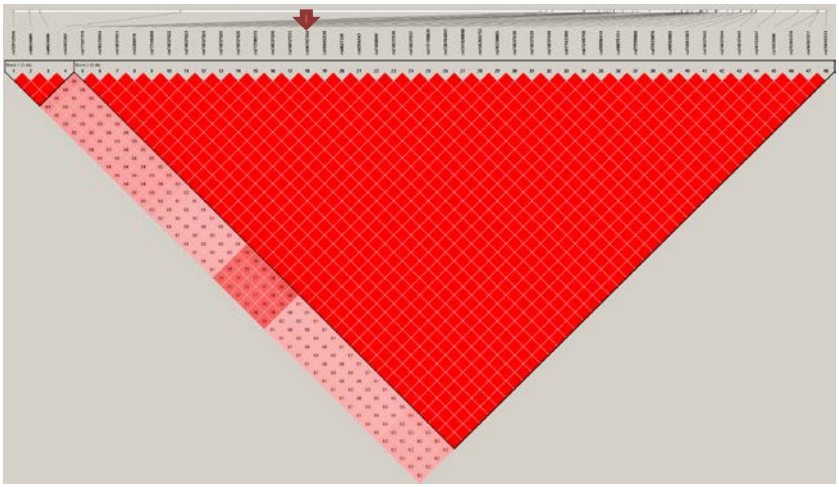


Figure 3.4. Regional plot and LD plot for Cooperativeness and rs56197244

2.2. Univariate Genome-wide association analysis for FFM

Average scores of each traits of FFM are shown in Table 3.3. The scores were significantly different between genders for agreeableness and conscientiousness, but not for neuroticism, extraversion, and openness to experience. The top 20 SNPs and their association results with lowest p-value for each dimension are displayed in Table 3.4. None of the SNPs were genome-wide significant, but for agreeableness, rs12926331 located within *CDH13* (cadherin 13) in chromosome 16 showed marginal significance (p=2.80E-07, H^2=2.66%). This SNP was replicated in the results from de Moor et al. (2012) [45] where p-value is 0.046 for association with agreeableness, but with different direction of effect (beta=-0.17 S.E.=0.087). Manhattan plots and Q-Q plots for all five traits of FFM are displayed in Figure 3.5 and 3.6. The SNPs that showed moderate association with agreeableness in CDH13 were all in LD (r^2 >0.6) with rs12926331 (Figure 3.7).

Table 3.3. Mean scores of the Five Factor Model traits, stratified across sex

	Men		Women		
	N	Mean(S.D)	N	Mean(S.D)	p value [a]
Neuroticism	476	51.47(8.77)	693	51.43(8.62)	0.94
Extraversion	476	58.21(8.18)	693	58.77(8.35)	0.2612
Openness to experience	476	58.19(8.15)	693	58.28(7.73)	0.85
Agreeableness	476	62.44(6.55)	693	63.84(7.08)	0.0005
Conscientiousness	476	61.67(7.39)	693	62.51(7.36)	0.06

[a] obtained by Student's t-test
All rounded to the nearest tenth
Abbreviations: S.D, Standard Deviation;

Table 3.4. Top 20 ranked SNPs associated with each Five-Factor Model dimensions

Openness to experience

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
3	rs1829551	T/C	ADGRG7	Intron	0.14	-2.77	0.55	4.02E-07
3	rs6793682	C/A	ADGRG7	Intron	0.14	-2.77	0.55	4.02E-07
3	rs9815749	C/T	ADGRG7	Intron	0.13	-2.61	0.57	3.77E-06
9	rs55834240	C/T		Intergenic	0.08	3.16	0.69	4.99E-06
9	rs72715622	T/C		Intergenic	0.08	3.16	0.69	4.99E-06
9	rs72715624	T/G		Intergenic	0.08	3.16	0.69	4.99E-06
9	rs72715625	G/C		Intergenic	0.08	3.16	0.69	4.99E-06
2	rs1876725	A/C		Intergenic	0.31	-1.95	0.43	5.13E-06
2	rs10185574	A/G		Intergenic	0.31	-1.94	0.43	5.64E-06
4	rs1369087	G/T	BMPR1B	Intron	0.36	1.76	0.39	5.80E-06
4	rs1369086	A/G	BMPR1B	Intron	0.36	1.76	0.39	6.11E-06
9	rs72715615	G/A		Intergenic	0.07	3.19	0.71	6.35E-06
9	rs7028869	C/G		Intergenic	0.07	3.19	0.71	6.36E-06
9	rs72715609	T/C		Intergenic	0.07	3.19	0.71	6.36E-06
4	rs6815866	C/G	BMPR1B	Intron	0.36	1.75	0.39	6.56E-06
4	rs6532532	T/C	BMPR1B	Intron	0.36	1.73	0.39	8.37E-06
3	rs6781584	C/T	TFG	Upstream	0.13	-2.50	0.56	8.98E-06
3	rs6441402	A/G	ADGRG7	Intron	0.12	-2.53	0.57	9.77E-06
3	rs7629279	G/T	ADGRG7	Intron	0.12	-2.53	0.57	9.82E-06
4	rs1434547	T/C	BMPR1B	Intron	0.35	1.73	0.39	1.01E-05

Conscientiousness

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
13	rs1980747	A/G	EIF4A1P7	Downstream	0.20	-1.99	0.43	3.44E-06
2	rs881184	G/T		Intergenic	0.06	-3.45	0.75	4.43E-06
13	rs4769625	T/C		Intergenic	0.24	-1.89	0.42	5.95E-06
13	rs2153572	G/A		Intergenic	0.24	-1.89	0.42	5.95E-06
2	rs6721673	A/T		Intergenic	0.07	-3.26	0.73	8.57E-06
11	rs2299623	A/G	SERGEF	Intron	0.35	-1.67	0.38	9.49E-06
11	rs3958112	G/T	SERGEF	Intron	0.35	-1.67	0.38	9.49E-06
2	rs7595798	G/A		Intergenic	0.07	-3.23	0.73	9.60E-06
2	rs6715405	A/G		Intergenic	0.07	-3.23	0.73	9.61E-06
13	rs7990417	T/C		Intergenic	0.17	-2.02	0.46	9.62E-06
13	rs9579208	A/G		Intergenic	0.17	-2.02	0.46	9.62E-06
2	rs4972370	G/A		Intergenic	0.07	-3.23	0.73	9.62E-06
2	rs4972371	T/C		Intergenic	0.07	-3.23	0.73	9.62E-06
13	rs9314915	G/C		Intergenic	0.17	-2.02	0.46	9.63E-06
16	rs8045933	A/G		Intergenic	0.46	-1.63	0.37	1.01E-05
16	rs8045914	A/G		Intergenic	0.46	-1.63	0.37	1.01E-05
16	rs7184508	C/T		Intergenic	0.46	-1.62	0.37	1.14E-05
13	rs1754963	A/C	Y_RNA	Downstream	0.18	-1.99	0.45	1.16E-05
13	rs1771173	G/A	Y_RNA	Downstream	0.18	-1.99	0.45	1.16E-05
13	rs1771172	A/G	Y_RNA	Downstream	0.18	-1.99	0.45	1.16E-05

Extraversion

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
9	rs140954641	A/G		Intergenic	0.03	5.36	1.14	2.74E-06
14	rs10142144	C/T	ERH	Downstream	0.21	-2.24	0.49	5.00E-06
14	rs8015425	G/A		Intergenic	0.21	-2.23	0.49	5.12E-06
14	rs897330	T/G		Intergenic	0.21	-2.23	0.49	5.28E-06
14	rs10083335	C/T		Intergenic	0.21	-2.22	0.49	5.39E-06
14	rs56953348	C/G	SLC39A9	Intron	0.21	-2.20	0.49	6.13E-06
14	rs11622711	T/C	SLC39A9	Intron	0.21	-2.20	0.49	6.14E-06
14	rs7145944	T/C	SLC39A9	Intron	0.21	-2.20	0.49	6.14E-06
14	rs7147362	C/G	SLC39A9	Intron	0.21	-2.20	0.49	6.14E-06
14	rs7147710	G/A	SLC39A9	Intron	0.21	-2.20	0.49	6.14E-06
14	rs12878175	G/A	SLC39A9	Intron	0.21	-2.20	0.49	6.14E-06
14	rs1958121	T/C	SLC39A9	Intron	0.21	-2.20	0.49	6.14E-06
14	rs11624577	A/G	SLC39A9	Intron	0.21	-2.20	0.49	6.15E-06
14	rs34840252	C/T	SLC39A9	Intron	0.21	-2.20	0.49	6.15E-06
14	rs4899295	T/G	SLC39A9	Intron	0.21	-2.20	0.49	6.15E-06
14	rs10143593	G/A	SLC39A9	Intron	0.21	-2.20	0.49	6.15E-06
14	rs10140273	A/G	SLC39A9	Intron	0.21	-2.20	0.49	6.15E-06

14	rs8016781	A/T	SLC39A9	Intron	0.21	-2.20	0.49	6.15E-06
14	rs67502261	A/G	SLC39A9	Intron	0.21	-2.20	0.49	6.15E-06
14	rs2085193	C/T	SLC39A9	Intron	0.21	-2.20	0.49	6.16E-06

Agreeableness

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
16	rs12926331	C/T	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs12926342	C/A	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs12926347	C/G	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs12926452	G/A	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs13380527	C/T	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs13380528	G/A	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs13380530	G/A	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs13380665	C/T	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs16961361	G/A	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs35784951	C/T	CDH13	Intron	0.07	3.00	0.58	2.80E-07
16	rs13380526	A/C	CDH13	Intron	0.07	2.97	0.58	3.43E-07
16	rs10514594	T/C	CDH13	Intron	0.10	2.63	0.54	1.18E-06
19	rs62119264	C/G	IGSF23	Intron	0.12	2.53	0.53	1.50E-06
2	rs17031012	C/A	AC074391.1	Intron	0.22	-1.84	0.40	3.84E-06
2	rs993468	T/G	AC074391.1	Intron	0.22	-1.83	0.40	4.79E-06
2	rs993467	T/C	AC074391.1	Intron	0.22	-1.83	0.40	4.79E-06
2	rs993466	A/C	AC074391.1	Intron	0.22	-1.83	0.40	4.80E-06
2	rs976395	G/A	AC074391.1	Intron	0.22	-1.83	0.40	4.85E-06
20	rs13036883	C/T	RP1-122P22.2	Downstream	0.18	2.24	0.49	5.33E-06
20	rs7273419	A/G	RP1-122P22.2	Non-Coding Transcript	0.19	2.18	0.48	5.39E-06

Neuroticism

Chr	SNP	Alleles	Gene	Type	MAF	Beta	SE	P-value
10	rs1007042	T/G	STOX1	Intron	0.38	2.02	0.43	2.58E-06
5	rs17692371	G/A	CHSY3	Intron	0.38	-2.09	0.47	8.20E-06
5	rs2052007	G/A	CHSY3	Intron	0.38	-2.07	0.47	9.47E-06
5	rs73244849	G/A	CHSY3	Intron	0.38	-2.07	0.47	9.91E-06
5	rs73244841	A/G	CHSY3	Intron	0.38	-2.06	0.47	1.15E-05
5	rs17692333	G/A	CHSY3	Intron	0.38	-2.06	0.47	1.16E-05
5	rs10463863	G/T	CHSY3	Intron	0.38	-2.06	0.47	1.26E-05
5	rs17692341	C/T	CHSY3	Intron	0.38	-2.05	0.47	1.29E-05
3	rs13090184	C/T	PTPRG	Intron	0.10	3.02	0.69	1.33E-05
10	rs7087588	G/A		Intergenic	0.38	1.89	0.44	1.51E-05

14	rs11620802	A/C	CHGA	Upstream	0.12	3.13	0.73	1.56E-05
14	rs8003675	G/C	CHGA	Upstream	0.12	3.13	0.73	1.56E-05
18	rs962247	G/A		Intergenic	0.39	1.88	0.44	1.64E-05
18	rs4800216	G/T		Intergenic	0.39	1.87	0.43	1.66E-05
10	rs4320849	T/C	STOX1	Intron	0.38	1.84	0.43	1.72E-05
14	rs941586	C/A	CHGA	Intron	0.12	3.10	0.72	1.90E-05
14	rs9658628	G/A	CHGA	Upstream	0.12	3.10	0.73	1.94E-05
18	rs4800215	T/C		Intergenic	0.41	1.84	0.43	1.97E-05
3	rs7615655	T/C	PTPRG	Intron	0.10	2.99	0.70	1.98E-05
14	rs12878661	G/A	ITPK1	Downstream	0.11	3.10	0.73	2.02E-05

Abbreviations: Chr, Chromosome; SNP, single nucleotide polymorphism; MAF, Minor allele frequency; SE, Standard Error; Alleles – Major Allele/Minor Allele
All rounded to the nearest tenth

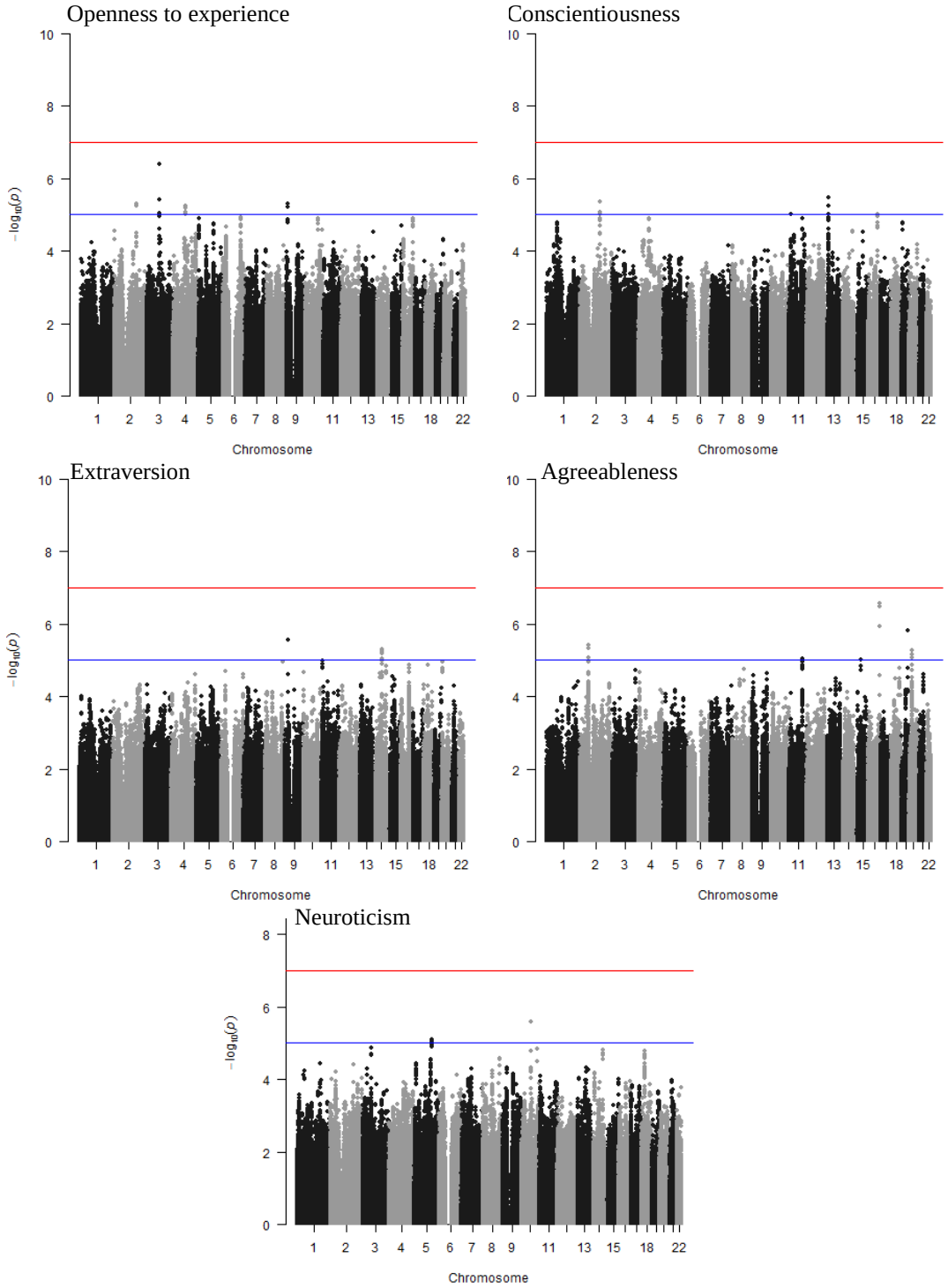


Figure 3.5. Manhattan plot for the association result of Five-Factor Model (FFM)

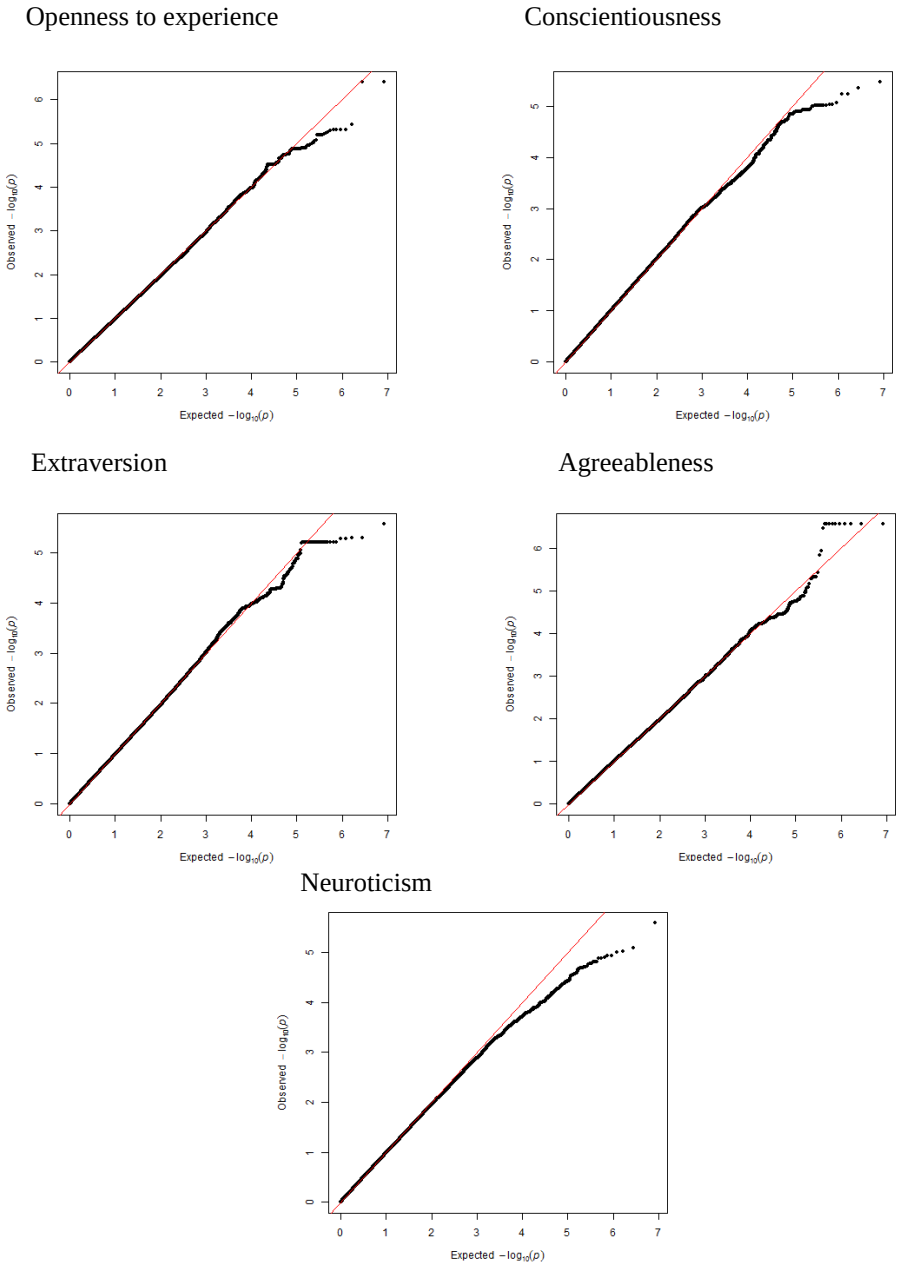


Figure 3.6. Q-Q plot for the association result of Five-Factor Model (FFM)

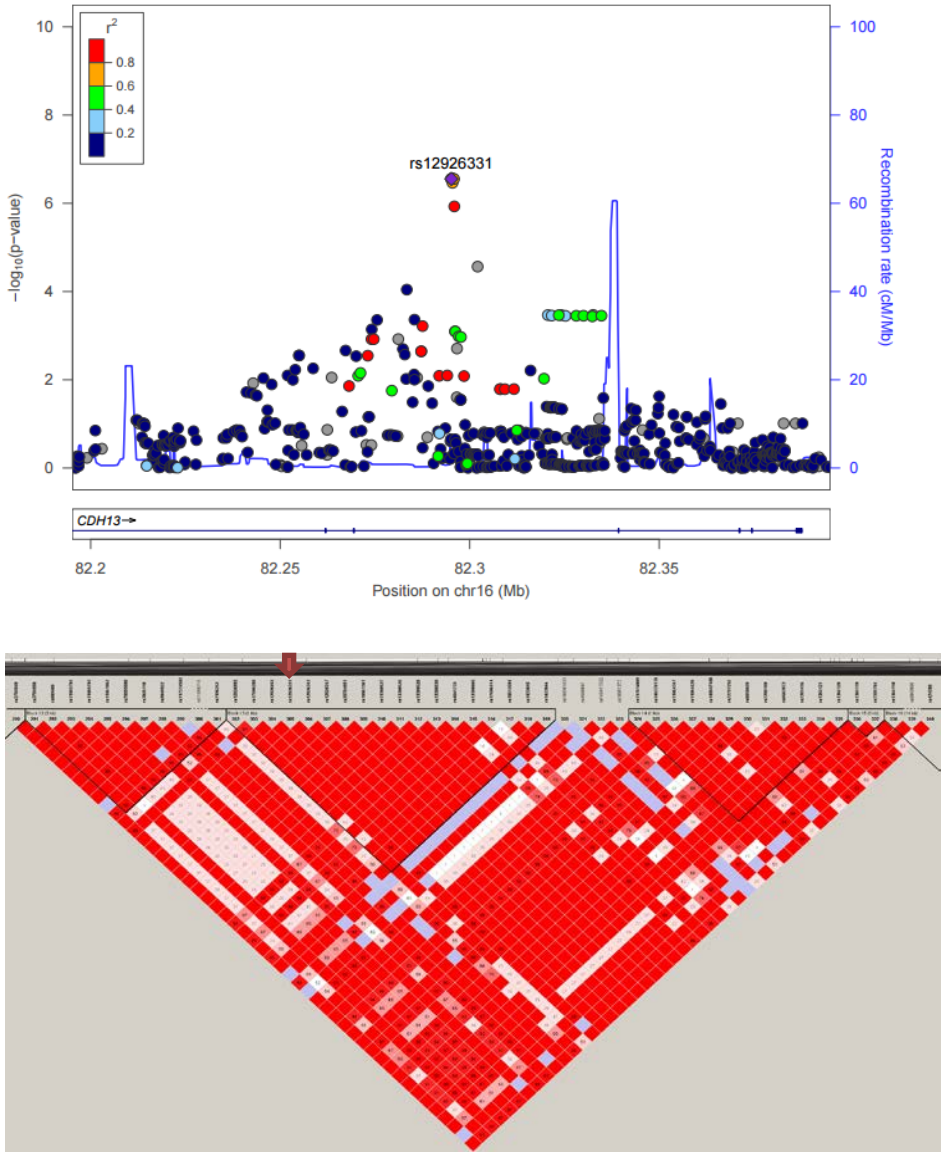


Figure 3.7. Regional plot and LD plot for Agreeableness and rs12926331

2.3. Multivariate Genome-wide association analysis for TCI and FFM

Table 3.5 shows the magnitude of correlation between traits of TCI and FFM. Despite their based psychological model of each factors being orthogonal (uncorrelated), modest inter-correlation is observed within same personality models. HA and neuroticism, SD and neuroticism, CO and agreeableness, PE and conscientiousness are the combination of traits that showed substantial correlation, with absolute value of correlation coefficient above 0.5 ($p < 0.0001$). For those trait pairs with correlation coefficient above 0.5, multivariate heritability analysis and multivariate family-based genome-wide association analysis was performed. The absolute estimation of genetic correlation were all above 0.75 for these trait pairs, indicating the presence of common genetic factors influencing multiple personality traits, and environmental correlation was 0.40~0.47 (Table 3.6). The top 20 ranked SNPs with lowest p-value for MFQLS statistics are shown in Table 3.7. Among the trait pairs that were examined, SD and neuroticism showed a genome-wide significant locus for *RP11-274B18.4* in chromosome 9 (top SNP= rs4745134, p-value=7.52E-09). *RP11-274B18.4* codes for long intergenic non-coding RNA (lincRNA) with no known function. Manhattan plot, Q-Q plot for SD-neuroticism association test are shown in Figure 3.8, and inflation factor for this trait pair was 1.02. The top 4 SNPs located in RP11-274B18.4 were all significant after multiple comparison of FDR, and 3 of these SNPs were still significant even after the strict Bonferroni correction (Table 3.8). In the regional plot (Figure 3.8) of rs4745134, remaining 3 SNPs with genome-wide significance were in high LD ($r^2 > 0.8$) with rs4745134.

Table 3.5. Correlation coefficients between Temperament and Character Inventory (TCI) and Five-Factor Model (FFM)

	NS	HA	RD	PE	SD	CO	ST	N	E	O	A	C
TCI												
NS	1	0.057*	0.222**	0.260**	-0.250**	-0.144**	0.360**	0.267**	0.202**	0.295**	-0.311**	-0.140**
HA		1	-0.168**	-0.338**	-0.690**	-0.321**	0.061*	0.546**	-0.483**	-0.194**	-0.058*	-0.288**
RD			1	0.168**	0.062*	0.373**	0.199**	0.077*	0.386**	0.155**	0.118**	0.006
PE				1	0.394**	0.303**	0.342**	-0.170**	0.362**	0.351**	-0.062*	0.540**
SD					1	0.299**	-0.040*	-0.562**	0.370**	0.195**	0.078*	0.450**
CO						1	0.211**	-0.300**	0.225**	0.206**	0.517**	0.221**
ST							1	0.101*	0.086*	0.312**	0.006*	0.084*
FFM												
N								1	-0.300**	-0.052	-0.250**	-0.393**
E									1	0.391**	0.072*	0.365**
O										1	0.050	0.282**
A											1	0.101*
C												1

**p<0.0001, *p<0.05

All rounded to the nearest hundredth

Adjusted for age and gender

Abbreviations: NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence; N, Neuroticism; E, Extraversion; O, Openness to experience; A, Agreeableness; C, Conscientiousness;

Table 3.6. Bi-variate heritability analysis of TCI and FFM, and estimates of their genetic/environmental correlation

			A(95%CI)	A(95%CI)	RhoG			RhoE	
TCI-FFM	n	r	TCI	FFM	estimate	p value*	p value**	estimate	p value
Harm Avoidance - Neuroticism	1163	0.55	0.29(0.18-0.40)	0.28(0.17-0.38)	0.76	7.83.E-07	6.76.E-04	0.47	1.65E-20
Self-Directedness - Neuroticism	1163	-0.56	0.33(0.23-0.44)	0.27(0.17-0.37)	-0.80	2.42.E-08	0.001	-0.47	3.03E-22
Cooperativeness - Agreeableness	1160	0.52	0.33(0.22-0.44)	0.30(0.19-0.40)	0.78	1.77E-08	0.001	0.40	8.89E-15
Persistence - Conscientiousness	1158	0.54	0.20(0.10-0.31)	0.22(0.1-0.33)	0.83	6.90.E-05	0.03	0.47	2.38E-23

Abbreviations: A, additive genetic effect estimates; CI, confidence interval; TCI, Temperament and Character Inventory; FFM, Five Factor Model; r, phenotype correlation coefficient; RhoG, genetic correlation; RhoE, environmental correlation;
Covariates used = age, sex, age2, age*sex, and age2*sex interactions
All rounded to the nearest tenth
*significance of the rhog parameter from zero
**significance of the rhog parameter from 1 or -1 (Test for pleiotropy)

Table 3.7. Top 20 SNPs from multivariate association analysis of TCI and FFM

Abbreviations: Chr, Chromosome; SNP, single nucleotide polymorphism; MAF, Minor allele frequency; SE, Standard Error; Alleles – Major Allele/Minor Allele
All rounded to the nearest tenth

Harm Avoidance - Neuroticism

Chr	SNP	Alleles	Gene	Type	MAF	P-value
18	rs67404903	T/A		Intergenic	0.39	2.50E-06
2	rs1526028	A/G	AC007246.3	Intron	0.04	2.77E-06
2	rs57584429	T/C	AC007246.3	Intron	0.04	2.77E-06
2	rs58306652	G/A	AC007246.3	Intron	0.04	2.77E-06
2	rs59735797	A/G	AC007246.3	Intron	0.04	2.77E-06
2	rs6717444	A/G	AC007246.3	Intron	0.04	2.77E-06
17	rs1533313	T/G	AIPL1	Intron	0.12	3.66E-06
18	rs882570	A/C		Intergenic	0.39	3.79E-06
2	rs10201923	T/C	AC007246.3	Intron	0.04	4.10E-06
2	rs73924265	G/C	AC007246.3	Intron	0.04	4.10E-06
17	rs1355877	C/A	AIPL1	Intron	0.12	4.11E-06
17	rs12451288	A/G	AIPL1	Intron	0.12	4.34E-06
17	rs9890415	G/T	AIPL1	Intron	0.13	4.45E-06
18	rs35963024	T/C		Intergenic	0.39	4.61E-06
17	rs8069471	C/T	AIPL1	Intron	0.13	4.80E-06
2	rs1608939	A/G	AC007246.3	Intron	0.04	5.64E-06
2	rs58977915	T/C	AC007246.3	Intron	0.04	5.64E-06
2	rs7586736	T/C	AC007246.3	Intron	0.04	5.64E-06
18	rs4800216	G/T		Intergenic	0.39	5.85E-06
18	rs66952120	A/T		Intergenic	0.39	6.27E-06

Self-Directedness - Neuroticism

Chr	SNP	Alleles	Gene	Type	MAF	P-value
9	rs4745134	T/C	RP11-274B18.4	Intron	0.25	7.52E-09
9	rs4745135	T/C	RP11-274B18.4	Intron	0.25	7.52E-09
9	rs11143037	C/T	RP11-274B18.4	Intron	0.25	1.91E-08
9	rs1888722	G/T	RP11-274B18.4	Intron	0.25	4.15E-08
1	rs2458525	A/G	SPATA21	Intron	0.11	1.93E-06
1	rs525409	C/G	SPATA21	Missense	0.11	3.40E-06
1	rs612727	C/T	SPATA21	Intron	0.12	3.69E-06
1	rs6603860	C/T	SPATA21	Downstream	0.11	3.69E-06
5	rs7713943	G/T		Intergenic	0.19	3.74E-06
5	rs6596436	G/C		Intergenic	0.21	3.76E-06
5	rs11242428	A/G		Intergenic	0.21	3.86E-06
5	rs11242429	T/C		Intergenic	0.21	3.86E-06
5	rs11242430	C/A		Intergenic	0.21	3.86E-06
5	rs6596435	C/G		Intergenic	0.21	3.86E-06

5	rs6870458	G/T		Intergenic	0.21	3.86E-06
5	rs6885225	T/C		Intergenic	0.21	3.86E-06
5	rs219277	C/T		Intergenic	0.21	4.39E-06
5	rs219278	G/A		Intergenic	0.21	4.39E-06
5	rs10793824	C/T		Intergenic	0.20	4.46E-06
5	rs6887341	G/A		Intergenic	0.20	4.46E-06

Cooperativeness - Agreeableness

Chr	SNP	Alleles	Gene	Type	MAF	P-value
16	rs12926331	C/T	CDH13	Intron	0.07	9.37E-07
16	rs12926342	C/A	CDH13	Intron	0.07	9.37E-07
16	rs12926347	C/G	CDH13	Intron	0.07	9.37E-07
16	rs12926452	G/A	CDH13	Intron	0.07	9.37E-07
16	rs13380527	C/T	CDH13	Intron	0.07	9.37E-07
16	rs13380528	G/A	CDH13	Intron	0.07	9.37E-07
16	rs13380530	G/A	CDH13	Intron	0.07	9.37E-07
16	rs13380665	C/T	CDH13	Intron	0.07	9.37E-07
16	rs16961361	G/A	CDH13	Intron	0.07	9.37E-07
16	rs35784951	C/T	CDH13	Intron	0.07	9.37E-07
16	rs10514594	T/C	CDH13	Intron	0.10	1.18E-06
16	rs13380526	A/C	CDH13	Intron	0.07	1.25E-06
12	rs10093747	C/T		Intergenic	0.02	1.33E-06
12	rs11615647	C/T		Intergenic	0.02	1.33E-06
12	rs117271411	G/T		Intergenic	0.02	1.33E-06
12	rs139360458	T/A		Intergenic	0.02	1.33E-06
12	rs141728502	C/T		Intergenic	0.02	1.33E-06
12	rs142800628	C/T		Intergenic	0.02	1.33E-06
12	rs145003163	G/A		Intergenic	0.02	1.33E-06
12	rs145698922	C/G		Intergenic	0.02	1.33E-06

Persistence - Conscientiousness

Chr	SNP	Alleles	Gene	Type	MAF	P-value
20	rs2426668	C/T	RP5-897D18.1	Upstream	0.23	1.17E-06
20	rs6069846	T/A	RP5-897D18.1	Downstream	0.24	1.64E-06
20	rs2208525	G/T	RP5-897D18.1	Non-Coding Transcript	0.24	2.01E-06
4	rs116529063	G/C	RP11-431M7.2	Intron	0.23	4.83E-06
20	rs2426664	G/A		Intergenic	0.23	7.04E-06
20	rs2426661	G/A		Intergenic	0.23	7.68E-06
20	rs4811744	C/A	RP5-897D18.1	Upstream	0.23	7.94E-06
1	rs143287206	C/T	ST7L	Downstream	0.06	1.01E-05
4	rs16992173	T/C	RP11-431M7.2	Intron	0.23	1.04E-05
4	rs10517374	T/A	RP11-431M7.2	Intron	0.24	1.08E-05
4	rs16992175	T/C	RP11-431M7.2	Intron	0.24	1.08E-05
6	rs598286	G/A	EYA4	Intron	0.43	1.10E-05
6	rs212771	T/C	EYA4	Intron	0.43	1.22E-05
4	rs150689744	G/A	RP11-431M7.2	Intron	0.23	1.37E-05
4	rs16992168	T/C	RP11-431M7.2	Intron	0.23	1.37E-05
4	rs28410841	C/G	RP11-431M7.2	Intron	0.23	1.37E-05
4	rs59386807	T/C	RP11-431M7.2	Intron	0.23	1.37E-05
4	rs28414714	G/A	RP11-431M7.2	Intron	0.23	1.61E-05

4	rs77696754	C/T	RP11-431M7.2	Intron	0.23	1.61E-05
4	rs80290770	A/G	RP11-431M7.2	Intron	0.23	1.61E-05

Table 3.8. P-values after multiple comparisons for Self-Directedness – Neuroticism multivariate analysis

Chr	SNP	Gene	P-value	FDR	BonF
9	rs4745134	RP11-274B18.4	7.52E-09	0.02	0.03
9	rs4745135	RP11-274B18.4	7.52E-09	0.02	0.03
9	rs11143037	RP11-274B18.4	1.91E-08	0.03	0.08
9	rs1888722	RP11-274B18.4	4.15E-08	0.04	0.17
1	rs2458525	SPATA21	1.93E-06	0.58	1.00
1	rs525409	SPATA21	3.40E-06	0.58	1.00
1	rs612727	SPATA21	3.69E-06	0.58	1.00
1	rs6603860	SPATA21	3.69E-06	0.58	1.00
5	rs7713943		3.74E-06	0.58	1.00
5	rs6596436		3.76E-06	0.58	1.00
5	rs11242428		3.86E-06	0.58	1.00
5	rs11242429		3.86E-06	0.58	1.00
5	rs11242430		3.86E-06	0.58	1.00
5	rs6596435		3.86E-06	0.58	1.00
5	rs6870458		3.86E-06	0.58	1.00
5	rs6885225		3.86E-06	0.58	1.00
5	rs219277		4.39E-06	0.58	1.00
5	rs219278		4.39E-06	0.58	1.00
5	rs10793824		4.46E-06	0.58	1.00
5	rs6887341		4.46E-06	0.58	1.00

Abbreviations: Chr, Chromosome; SNP, single nucleotide polymorphism; FDR, False Discovery Rate; BonF, Bonferroni correction;
All rounded to the nearest tenth

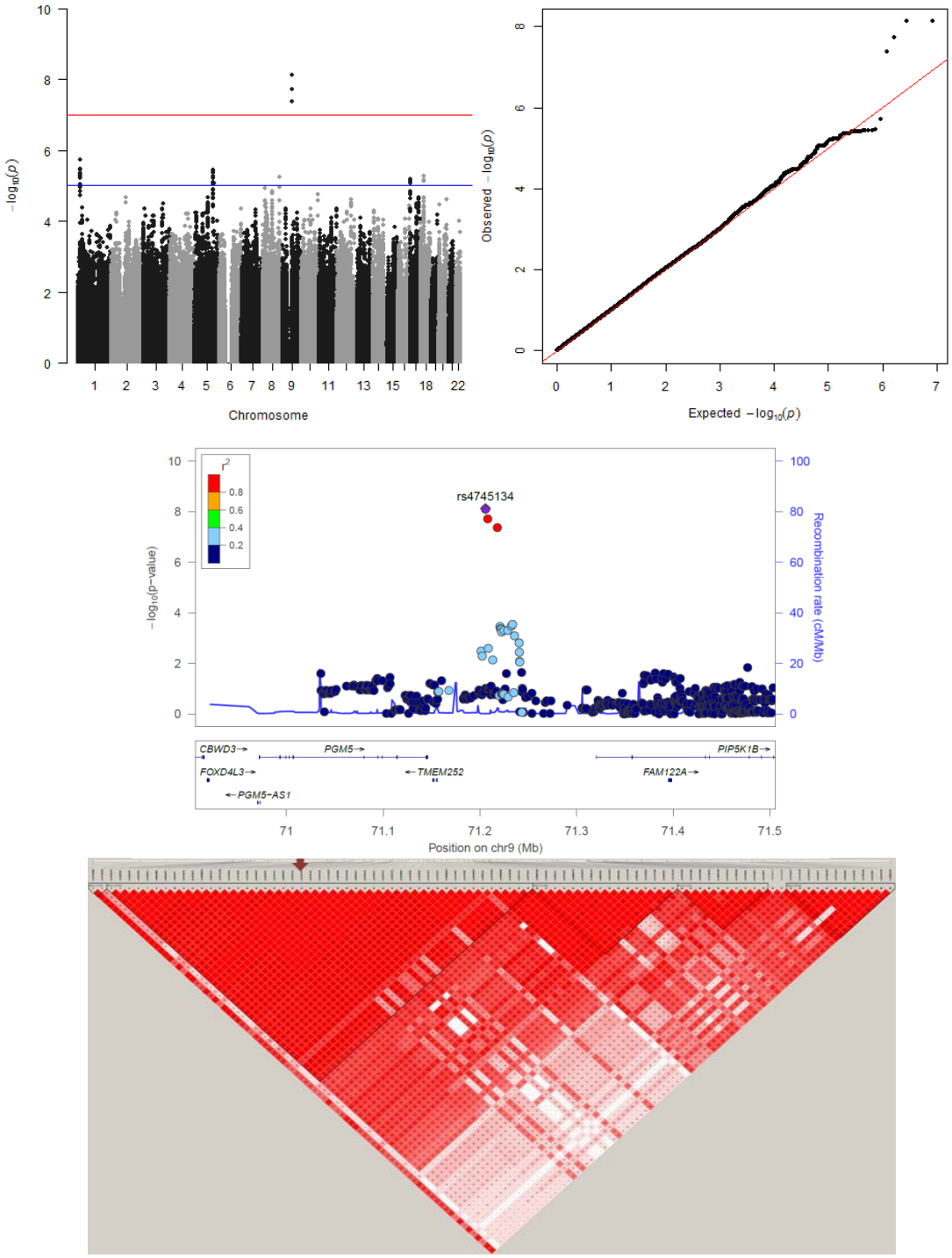


Figure 3.8. Manhattan plot, Q-Q plot, regional plot, and LD plot of rs4745134 for the multivariate association result of Self-directness of TCI and Neuroticism of FFM

2.4. Replication with previously reported personality-associated genetic variants

There are several reported genetic variants from large-scale consortium studies that need to be replicated in an external study. de Moor et al.(2012) [45] reported that two SNPs in *RASA1* gene (rs1477268, rs2032794) and one SNP in *KATNAL2* (rs2576037) was observed to be genome-wide significantly associated with openness to experience and conscientiousness respectively, but failed to replicate the result in Caucasian samples. P-values for these SNPs were compared with current study's results. For *RASA1* gene (rs1477268, rs2032794), p-values for openness was close to 0.05 (p=0.056, 0.056), and p-values for persistence of TCI was 0.041 and 0.033 for these SNPs. Openness to experience and persistence is modestly correlated in our data (r=0.351). Results for *KATNAL2* SNP was not significantly replicated in our study (p=0.325). Recently published GWAS on extraversion [47] reported a suggestive novel locus on *LOC1019282*, but the same SNP was not significant for extraversion in this study as well (p=0.751). Another reported genome-wide significant variant for neuroticism is rs35855737 in *MAGI1* [48]. However this SNP was not available in our data and other SNPs with p-value less than 0.05 in *MAGI1* gene was not in LD with rs35855737. The top SNPs with marginal significance from meta-analysis of temperament traits [44] as well as meta-analysis on Korean FFM [46] were also not replicated in our data. The SNPs that exceeds genome-wide significance threshold in our study were not examined (rs56197244) or replicated (rs4745134) in meta-studies of FFM [45, 47, 48], where results of all SNPs were available for use.

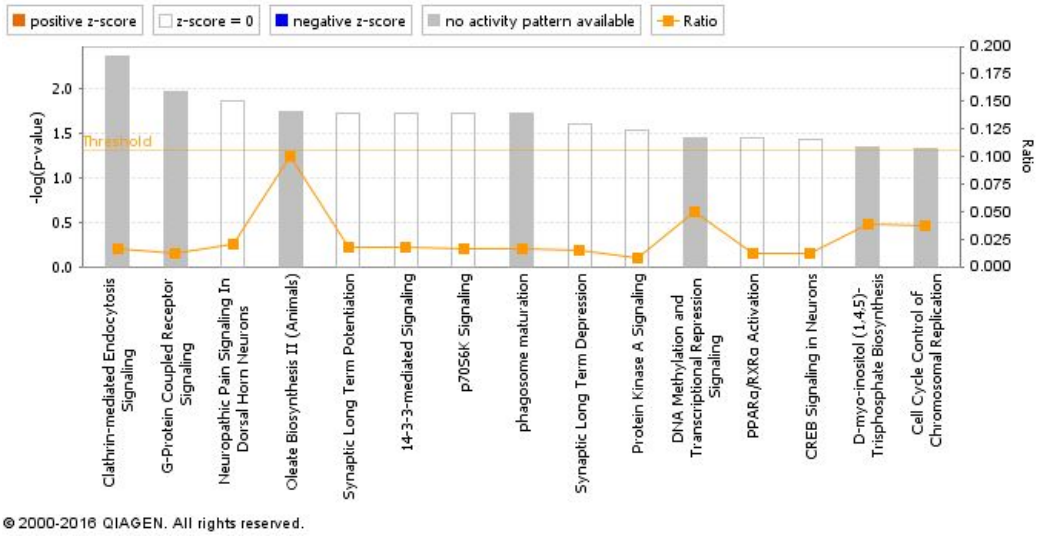
2.5. Pathway Analysis

All SNPs with p-value <0.0001 from association analysis for cooperativeness and self-directedness-neuroticism were tested for their representation at a known biological or canonical pathways, using the Ingenuity Pathway Analysis program (IPA, Ingenuity Systems, CA, USA). Total of 632 variants from 51 molecules were included for cooperativeness, and 736 variants of 55 molecules for self-directedness-neuroticism was include in this analysis. Results from canonical pathway analysis are displayed in Figure 3.9, but none of the pathways remained significant after Benjamini-Hochberg Multiple Testing Correction.

2.6. Different level of variances explained for personality traits

Estimated variance explained from the reported pedigree, common SNPs, and a top SNP from each GWA-analysis is compared in Figure 3.10. For TCI, heritability estimates estimated from reported pedigree of the samples (reported in Chapter 2) ranged 15~44%, whereas variance explained by additive effects of common SNPs were as low as 0.4% in PE, and ST showed highest estimate of 13.9%, but the estimates from common SNPs were very small compared to the h^2 from pedigree data. Also the variance explained by GWAS top SNP was 0.9~1.2% which indicates polygenic effect of common variants for personality traits and the phenomenon of the “missing heritability”. Similar estimates were also observed for the traits of FFM.

<Cooperativeness>



<Self-directedness and Neuroticism>

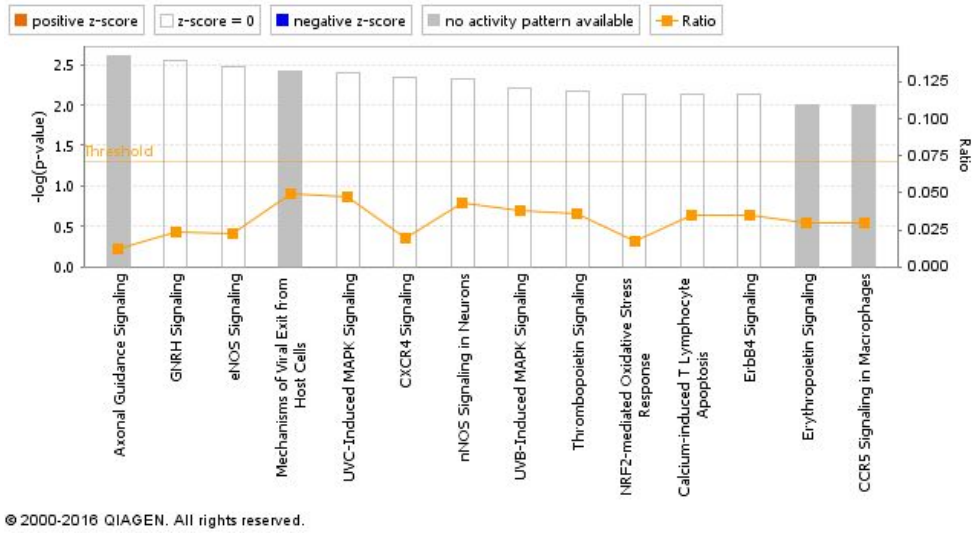


Figure 3.9. Top canonical pathways with Fisher's exact test p-value < 0.05 (0.01 for Self-Directedness - Neuroticism for display purpose) from the pathway analysis using Ingenuity Pathway Analysis program (IPA, Ingenuity Systems, CA, USA)

Definition: Ratio- # of genes in a given pathway that meet cutoff criteria over total # of genes in a pathway from the reference gene set; Z-score – used for mathematical comparison of uploaded dataset with the canonical pathway patterns. Positive score indicate predicted pathway activation, negative score indicate pathway inhibition.

All results from this pathway analysis were not significant after correcting for multiple comparisons.

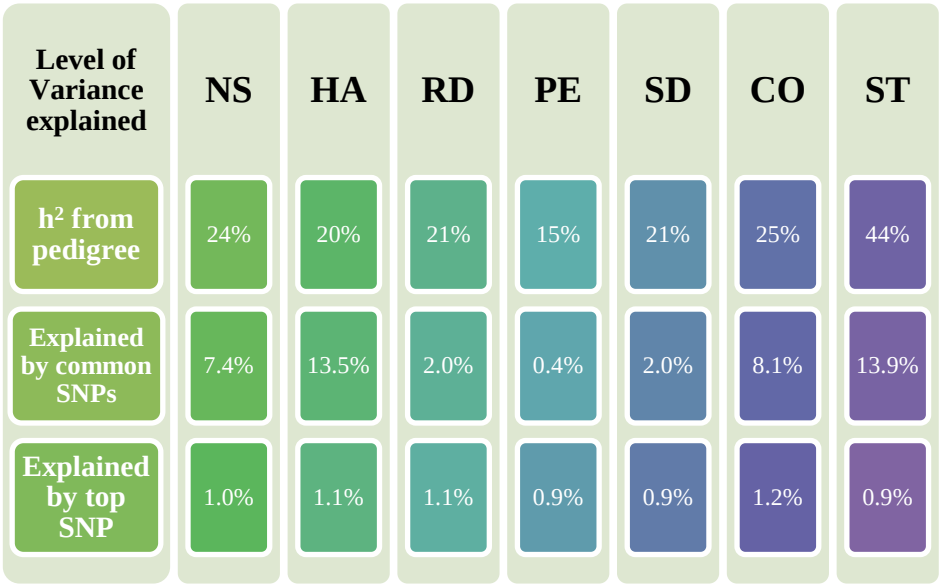


Figure 3.10. Level of Variance explained for Temperament and Character Inventory and Five-Factor Model
* estimated using the Health Twin study from Kim et al. , 2015 [46]

3. Discussion

This study analyzed various personality traits from two different psychological model of personality – Temperament and Character Inventory (TCI) and Five Factor model (FFM), which are the most widely used taxonomies in the field of behavioral genetics. Two novel loci and one replicated locus that may be associated with some dimensions of personality in a Korean population were found from the study results. From the univariate analysis of each independent personality dimensions, *ADAMTS17* was discovered as the related gene of cooperativeness of TCI with genome-wide significance. *ADAMTS17* is a protein coding gene, and is associated with Weill-Marchesani-like syndrome, which is a rare disorder of connective tissue, and Ichthyosis-short stature-brachydactyly-microspherophakia syndrome, which is a type of rare congenital malformation disorder. The protein encoded from this gene is a member of the protein family related to metalloendopeptidase activity, which is a group of enzymes that catalyze the splitting of polypeptide chains. ADAMTS protein family is a key remodeling enzymes of the extracellular matrix and plays a role in connective tissue organization, coagulation, inflammation and etc. [118]. The exact function of protein coded by *ADAMTS17* gene has not been determined, but the protein family has been reported to be involved in neural plasticity [119]. Also for agreeableness in FFM, *CDH13* had borderline genome-wide significance (p=2.80E-7), and the genetic variant was replicated in de Moor et al.(2012)'s study [45]. *CDH13* encodes cadherin superfamily, and this protein is known to act as a negative regulator of axon growth during neural differentiation.

However the direction of the allele's additive effect was opposite, indicating some chance of false-positive finding.

Furthermore, in multivariate genome-wide association analyses for trait pairs, each trait from TCI or FFM, were conducted to further discover the genetic variant related to personality traits. Only the trait pairs that have high correlation (absolute r >0.5) were selected for this analysis, and for self-directedness-neuroticism, genome-wide significant locus was observed. *RP11-274B18.4* in chromosome 9 showed strong signal for the association, but there is no known function for this long intergenic non-coding RNA. There was no canonical pathway that was associated with SNPs with p-value < 0.0001 from the GWA results.

TCI and FFM is based on different school of psychology, and because their highest correlation does not exceed 0.6, which is also similar in De Fruyt et al. (2000)'s report [120], they are not suitable for meta-analysis where simple sum values of each traits are used [44]. Instead, more sophisticated approach such as harmonizing traits using item response theory [47, 121], or multivariate approach can be used. By performing the multivariate analysis of personality traits that are highly genetically correlated (>0.75), a novel locus that may be associated with human personality with strong significance (p-value= 7.52E-09) was located in our sample, which is comprised of relatively smaller subjects than the meta-analysis study on neuroticism or extraversion with more than 63,000 study sample (lowest p-value for neuroticism=9.26E-9). However, due to scarcity of samples with both TCI and FFM measures, the current study face difficulty in finding the

exact replication for this locus.

Structural genetic difference between different populations may explain why it was difficult to find the overlapping genetic locus with reported personality associated genetic variants in Caucasian samples. The reported *RASA1* gene that is associated with openness to experience [45] had borderline p-value in our study, and persistence of TCI had association with this genetic variant at an alpha level of 0.05 instead. The correlation between these two traits were modest (r=0.38), which might explain the replication. However the results from Korean meta-analysis of FFM [46] were not replicated in current study, where subsamples of this study were used for replication, and top results from our study was also not listed in the top 100 ranked SNPs from Kim et al. (2015). Only the temperament scales of TCI was used for large-scale Meta-analysis [44], and the top SNPs from this study was also not significant in our results. However, from our analysis on heritability (Chapter 2, [80]) and many other heritability studies on personality [34-37, 40], it was proven that the magnitude of heritability is similar between temperament and character despite its initial hypothesis. By testing all dimensions of TCI, the novel genetic locus with genome-wide significant association in cooperativeness and self-directedness (paired with neuroticism of FFM) of character trait were discovered, but not among temperament traits.

One of the limitations of this study is, because many traits of personality from two different personality model and their combinations were tested (total of 16 separate analysis), more stringent multiple testing might need to be applied for interpretation of the results. However many studies

assessing the association between genome-wide variants and a phenotypes sets p-value of 5×10^{-8} as a threshold [122], and Panagiotou et al. (2012) [123] reported that borderline genome-wide significances were sufficient for replication, suggesting possible relaxation in the threshold for GWA studies. Another limitation can be a relatively small size of the study participants compared to highly powered consortium studies of personality, and lack of replication data due to scarcity of East Asian genetic studies with both genotype and personality traits available. Because there are different genetic background such as minor allele frequencies and linkage disequilibrium patterns among different ethnicities, comparing the results of Caucasians directly to the results of East Asians might need some caution. However despite the relatively small sample size, this study were able to find loci associated with personality that exceeds the p value of genome-wide threshold, where even highly powered studies with more than 63,000 samples were not very successful. Lastly, because personality traits are self-administered using a set of questionnaires and due to language interpretation, bias can be introduced during the measurement. However validation of the personality inventories used in this study has been proven [84, 98], and many studies have confirmed their heritable properties.

The identical conclusions of many published studies [44, 45, 47, 48, 124] are that regardless of tools measuring the personality, it is difficult to find a strong signaled locus associated with personality using the standard approaches. From the results of these studies, the conclusion that personality traits are highly polygenic where many genes with very small effect explain

the variance of personality altogether can be made, and emphasis on new approach is highlighted. It has been reported that additive effect of common SNPs explain only about 12% of variance of the extraversion [49], 14.7% of neuroticism [48], and average of 7.2% of TCI's temperament dimensions [125], which much smaller than heritability estimates from pedigree and are constant with our results. These findings suggest that non-additive genetic component, such as dominance effect or epistasis, and/or rare alleles may contribute to large proportion of variation in personality. In fact, from the heritable analysis from Chapter 2, non-additive genetic influences ranged from 0.18 to 0.28 on personality traits measured by TCI, and for HA and PE, higher estimates for non-additive component than the additive component was observed. Because GWA methods are designed to analyze the additive effect of genetic variants, method estimating the effect of non-additive between variants should be considered in further study.

In conclusion, this study was able to find two new genetic loci of *ADAMTS17* and *RP11-274B18.4*, and one suggestive replicated region of *CDH13* that might help us to further understand the genetics of personality and etiology of neurological, behavioral disorders. Our findings suggest that 1) some personality domains, particularly character traits have genetic or biological background in Koreans, and 2) not a single measure, but a multiple measures of personality traits might better capture the genetic architecture of personality traits. Because genetic studies on personality in Asian populations and studies which measured both TCI and FFM are scarce, the study currently awaits collaborations to replicate the findings.

IV. Personality and gene x personality (G x P) s' effect on Risky Health Behaviors

1. Targeted Health Behaviors and Previous Studies

Many studies linking personality and health or well-being of individuals have been conducted, especially on wide range of health behaviors that lead to harmful consequences [65, 126, 127]. Additionally, as stated in the Introduction, personality is an important factor in many proposed health behavior models [59, 60]. In this study, three health behavior related traits are targeted, which are especially based on psychological schemes; problematic eating behavior, nicotine dependency, and alcohol dependency.

Several studies on personality and body mass index (BMI) have reported conflicting results in their relationship, and most them concluded that personality alone does not have any significant role in increasing the BMI level, but reported associations with binge eating behaviors or diet patterns. [128-130]. Dalle Grave et al. (2014) [131] reported that obese individuals do have distinctive personality profile of low SD and CO, and obese individuals with binge eating behaviors had lower SD and higher NS and HA than ones without binge eating behavior, indicating personality's role in gaining weight through engagement in risky eating behavior. Problematic eating behaviors among Korean general population, represented by 199 medical students, was also associated with high HA, ST, and low SD [132]. Additionally, individuals with lower NS were more successful in losing weight [24] and personality traits were the significant predictors of adiposity in a prospective study [133], which suggests importance of utilizing personality traits in a clinical treatment or prevention approaches for obesity.

Additionally, profiles of personality differed among the sub-types of alcoholic patients [134]. Compared to healthy controls, alcohol dependent patients had higher NS and lower SD. Also, early-onset alcoholics were associated with higher NS and had lower scores of SD and CO than late-onset patients. NS likewise well predicted individual's alcohol-related problems among university students implying benefits of using personality in screening and treating excessive alcohol drinking and dependency [135]. When the several measures of personality dimensions were factorized into broad personality patterns, disagreeable disinhibition and unconscientious disinhibition, both with high loadings of NS, well predicted alcohol consumption [136]. Similar to alcohol related behaviors, smoking habits were associated with personality traits [137]. Daily smokers had higher NS when compared to non-smokers, and level of tobacco dependence was associated with higher scores of HA and lower SD [138]. Personality profiles were also reported to have influence on substance use [139] and choice of drugs [140], and NS, SD, and CO especially showed significant relationship to most of the risky health behaviors or dependencies.

Evidenced by many previous studies, NS, SD, and CO may play an important role in development of risky health behaviors that are associated with wide ranges of disease or health conditions. NS, which is suggested to be related to dopaminergic activity, has four subscales; NS1: Exploratory excitability, NS2: Impulsiveness, NS3: Extravagance, NS4: Disorderliness. Individuals with high NS are vulnerable to novel stimuli and tend to make impulsive decisions and avoid frustrations. A character trait SD defines one's

self-determination and regulation with five subscales: SD1: Responsibility, SD2: Purposefulness, SD3: Resourcefulness, SD4: Self-acceptance, SD5: Enlightened second nature. Lower scores of SD indicate a personality that is blaming, self-striving, passive, and lacks in goal direction and control. Another character dimension CO measures psychological maturity and reflects how a person engages in social relationships. There are five subdomains of CO; CO1: Social acceptance, CO2: Empathy, CO3: Helpfulness, CO4: Compassion, CO5: Principles [13]. Low scores of SD and CO are well known common factor in most of the personality disorders [26], thus suggesting relationship to problematic health behaviors as well.

Following are the description of the questionnaires that were used to evaluate each of the targeted traits that represents individual's problematic health behaviors.

2. Materials and Methods

2.1. Measurement of eating behavior and obesity

Body mass index (BMI), calculated as body weight divided by the square of the height (kg/m^2) was used as a tool to evaluate the level of obesity. In order to evaluate individual's eating behavior, the psychosomatic theory based Dutch Eating Behavior Questionnaire (DEBQ) [141] was used. DEBQ has three distinguished domains which are retrained, emotional, and external eating. Restrained eating domain measures individual's cognitive restraint on food intake to prevent weight gain, and is associated with higher and lower

body weights [142, 143]. Emotional eating is defined as a tendency of overeating as a reaction to negative emotions such as depression, anxiety, and etc. Lastly, external eating based on externality theory that represents the tendency of excessive intake of food stimulated by external food cues. DEBQ is known to be an indicator of eating disorders such as binge-eating disorder, bulimia and anorexia nervosa [144, 145], and obesity [146]. Relationships between theses eating behavior domains and personality has been reported [147] and heritable components of eating behaviors were also reported [148].

For the participant of the Healthy Twin study, 33 self-administered DEBQ questionnaires on 5 point Likert scale were used, comprising 10 items for restrained and external eating, and 13 items for emotional eating. The validation of the translated Korean version of DEBQ has been confirmed previously [149]. A total of 3,444 individuals completed this survey and the responses were reviewed by examiners at the recruiting hospitals.

2.2. Measurement of smoking behavior and nicotine dependency

The participants of the study were asked if they were ever an occasional cigarette smoker. For those who have answered that they are a current or former smoker, information on average number of cigarettes smoked per day and the number of years smoked were collected. Pack-Year was then calculated as number of packs (20 cigarettes) per day multiplied by the years smoked.

In order to measure the degree of dependency on cigarettes, the Fagerstorm Test for Nicotine Dependence (FTND) [150] was used. FTND is a

standard instrument that measures nicotine dependence, and individuals with high FTND scores are known to have difficulty in achieving successful cessation in cigarette smoking [151]. There are 6 items in the FTND, and questions asked are such as ‘How soon after waking do you smoke your first cigarette?’, ‘Do you find it difficult to refrain from smoking in places where it is forbidden?’, and etc. The response of each items were summed by the protocol to calculate the score for FTND. Total of 1,192 participants of the Healthy Twin study completed this test, and the validity of Korean version was reported elsewhere [152].

2.3. Measurement of alcohol intake and alcohol dependency

The participants were asked whether they have ever occasionally consumed an alcoholic beverage during their lifetime. They were also asked for the average frequency of occasions where different types of alcoholic beverages were consumed, the average number of alcoholic drinks consumed per each occasion, and the serving size of the drink was obtained. The beverage-specific amounts of ethanol consumed were calculated to determine the total weekly alcohol consumption (g/week).

As a measure for alcohol dependency and problematic drinking behaviors, Alcohol Use Disorders Identification Test (AUDIT) developed by World Health Organization [153] was used. This questionnaire contains 10 items on 0~4 point scale, and three of the item can be summed up to measure AUDIT consumption questions (AUDIT-C), which can be used as an effective screening for problematic drinking in medical settings [154]. In Korea, the

criteria for problem drinkers with both physical and psychosocial problems were 12~14 points [155]. Total of 2,441 individuals completed AUDIT-C, and 2,431 individuals completed the full AUDIT questionnaire.

2.4 Statistical Analysis

The general characteristics of the participants were compared between genders for BMI, three domains of DEBQ, smoking status, pack-year, FTND, alcohol drinking status, alcohol intake amount in g/week, AUDIT-C, and AUDIT, using Student's t-test for continues variables and chi-squared test for categorical variables. Scores of FTND, DEBQ-restrained eating (DEBQ-RSE), DEBQ-emotional eating (DEBQ-EME), AUDIT-C, and AUDIT were not normally distributed, and log transformation after adding a constant 1 was performed; DEBQ-external eating (DEBQ-EXE) was normally distributed and no further transformation was required.

Correlation coefficients between seven dimensions of TCI and the health behavior trait scores were estimated with age and gender adjusted residuals of scores to evaluate their resemblance. Mixed model was applied to adjust for random effect of familial correlations when analyzing association between personality and health behavior traits. Age, sex, education, and household income level were included as covariates in the multiple regression models for statistical adjustment. The proportion of variance of risky health behavior traits explained by each personality dimensions were estimated by maximizing polygenic model with and without (baseline) the variables in the model and comparing them using the variance decomposition method

implemented in SOLAR (Texas Biomedical Research Institute).

The personality scores were divided into three groups by their tertile, and linear contrast of mean scores of DEBQ, FTND, AUDIT-C and AUDIT were performed by the groups to see if there is a linear trend by personality in the health behavior traits. Age and gender were adjusted for this analysis. Relationships between successful smoking cessation and personality traits were also analyzed by comparing the average scores of TCI between individuals who stopped smoking and continued smoking. Successful cigarette quitter was defined as individuals who stated that they have quitted smoking or answered that they are current smoker in baseline visit, but as a former smoker when they re-visited the hospital for a follow-up.

From the results of association tests and previous studies on personality and health behaviors, it was identified that NS, SD, and CO are a strong significant predictors for overall health related behaviors. To see their combined effects on health behaviors, individuals were grouped by scores of various combinations of NS, SD, and CO. First, individuals were grouped into lower and higher scores of each dimension. For combinations of NS and SD, group 1, which is the group with low NS and high SD scores, were hypothesized to have lower average of health behavior traits; for group 4, composed of the individuals with high NS and low SD were hypothesized to have more risky health behavior. Group 2 and 3 are individuals with low NS and low SD, high NS and high SD, respectively, with hypothesis of having intermediate level of average health behavior scores compared to group 1 and

group 4. Same hypothesis were applied for NS- CO combination, and SD-CO (group 1 as high SD and high CO, group 4 as low SD and low CO). The group means were compared by analysis of variance (ANOVA) test adjusted for age, gender, and familial correlation using mixed model. The average scores of health behavior traits between group1 vs. group4, group 1, 2, 3 vs. group 4, and group 1vs. group 2, 3, 4 were also compared. In order to validate if the measured questionnaires well reflect problematic health behaviors, each scores were ranked, and was divided into tertile groups. Linear contrasts of mean scores of each tertile were performed for corresponding health behavior indicators using generalized linear model adjusted for age and gender; BMI with DEBQ domains, PY with FTND, g/week of ethanol with AUDIT-C and AUDIT.

In order to summarize the data into combination of multiple personality traits accounting for shared variance in the data, principal-axis factor (PAF) analysis was performed on sub dimensions of NS, SD, and CO. PAF method focuses on shared variance between multiple variables, and considers each variable's relationship to rest of the items. The factors with eigenvalue over 1 were retained. The oblimin rotation of the factors, which allows correlation between the components, was performed. The factors were all included in the multiple regression models to determine the factor pattern that best describes the variance of the health behavior data, and further association test were conducted for the selected factor pattern.

Using the 'pcalg' package in R [156], a completed partially directed

acyclic graph (CPDAG) was created. The method used for DAG generation was Peter Spirtes and Clark Glymou (PC) algorithm. This method starts the graph by fully connecting the nodes, and then based on judgments of conditional independency, adjacencies and directions are decided. For example, if a separating set that makes two nodes conditionally independent is present, the connecting edge is removed. The variables that were inputted in the model was Vulnerability, which is the most representable factor pattern associated with risky health behavior, income, education, BMI, and each risky health behavior traits. The health behavior traits were age and gender adjusted. Assuming that the DAG plotted from observation data is the true underlying DAG, the coefficient for causal effects of X on Y was obtained through simple linear regression. When Y is not a parent of X (if it is the estimated causal effect is assumed to be zero), regression coefficient of X is estimated from model Y=X+pa(X), where pa(X) is the parents of X. This estimation is provided from the same package, and can be obtained using 'ida()' option.

Using Vulnerability, prediction model was constructed in order to assess how much the personality can predict the presence of risky health behaviors. For test set, one individual of the MZ pair was randomly selected, and 1500 individuals were randomly selected from the rest of the pool. Rest of the samples and MZ twin were used for validation of the prediction model. For eating behaviors, upper tertiles of the DEBQ scores were defined as case. For FTND, score of 4 or over were considered as nicotine dependent [157], and for AUDIT, individuals with score higher than 12 were considered as alcohol dependents [155], and these individuals were considered as the cases

for the prediction.

The logistic regression was performed with age and Vulnerability, and the analysis was done separately for different genders. ROC (Receiver-Operating Characteristic)'s AUC (Area Under the Curve), which compares specificity and sensitivity, was computed to evaluate the model constructed, and in order to see if adding the Vulnerability to age-only model improves the prediction, NRI(Net Reclassification Improvement) and IDI(Integrated Discrimination Improvement) was estimated. NRI is an index that assesses how adding a new variable to a prediction model improves reclassification of subjects to case and controls. IDI compares discrimination slope, which is the probability differences in case and control groups, between models with and without Vulnerability [158].

Because personality is proximal to biological characteristics (i.e. gene) of individuals, personality is introduced as an intermediating phenotype affecting one's health behavior. In order to examine the gene-by-personality (GxP) effect on the targeted health behaviors, candidate gene lists were collected. Information on genetic variants related to neurodegenerative disease, neuro-psychological disorders or traits, and neurotransmitter activity were collected from Eu-pedia (http://www.eupedia.com/genetics/medical_dna_test.shtml) and SNPedia [159] resulting in 180 SNPs to be evaluated (sTable2). The novel SNPs found to be associated with personality in Chapter 3 were also included (rs12926331, rs4745134, rs56197244). For genetic analysis, age, sex, and familial correlation were adjusted using

GRAMMAR+ implemented in GenABEL package in R [160, 161]. The GRAMMAR+ transformation uses score statistics of linear regression mixed model, testing associations between trait and genotypes of given marker *m*. The score statistic is defined as following, where $\hat{\beta}_m$ and $Var(\hat{\beta}_m)$ are the effect of genetic marker *m* and its variance.

$$T^2_{Score,m} = \frac{\hat{\beta}^2_m}{Var(\hat{\beta}_m)}$$

To account for genetic relatedness among samples, they can be defined as following equation with Ω, which is a covariance matrix incorporating pairwise relationships. Here, N is the sample size, $\tilde{\mathrm{g}}_\mathrm{m}$ and $\tilde{\mathrm{y}}$ are vectors of centered genotype and phenotype values.

$$\hat{\beta}_{m,Score} = \frac{\tilde{\mathrm{g}}_\mathrm{M}^\mathrm{T}\Omega^{-1}\tilde{\mathrm{y}}}{\tilde{\mathrm{g}}_\mathrm{M}^\mathrm{T}\Omega^{-1}\tilde{\mathrm{g}}_\mathrm{m}}$$

$$Var(\hat{\beta}_{m,Score}) = \frac{\tilde{\mathrm{y}}^\mathrm{T}\Omega^{-1}\tilde{\mathrm{y}}}{\mathrm{N}(\tilde{\mathrm{g}}_\mathrm{M}^\mathrm{T}\Omega^{-1}\tilde{\mathrm{g}}_\mathrm{m})}$$

Then the transformation of the phenotype values is introduced as $y^{\oplus}$. For the transformation, the above expressions can be rewritten as following.

$$\hat{\beta}_{m,Score} = \frac{(\tilde{\mathrm{g}}_\mathrm{M}^\mathrm{T}\Omega^{-\frac{1}{2}})(\Omega^{-\frac{1}{2}}\tilde{\mathrm{y}})}{(\tilde{\mathrm{g}}_\mathrm{M}^\mathrm{T}\Omega^{-\frac{1}{2}})(\Omega^{-\frac{1}{2}}\tilde{\mathrm{g}}_\mathrm{m})}$$

$$T^2_{Score,m} = \frac{N[(\tilde{\mathrm{g}}_\mathrm{M}^\mathrm{T}\Omega^{-\frac{1}{2}})(\Omega^{-\frac{1}{2}}\tilde{\mathrm{y}})]^2}{(\tilde{\mathrm{g}}_\mathrm{M}^\mathrm{T}\Omega^{-\frac{1}{2}})(\Omega^{-\frac{1}{2}}\tilde{\mathrm{g}}_\mathrm{m})(\tilde{\mathrm{y}}^\mathrm{T}\Omega^{-\frac{1}{2}})(\Omega^{-\frac{1}{2}}\tilde{\mathrm{y}})}$$

The above formula is expressed with two notations, $\Omega^{-\frac{1}{2}}\tilde{\mathrm{g}}_\mathrm{m}$ and $\Omega^{-\frac{1}{2}}\tilde{\mathrm{y}}$. The vector $\Omega^{-\frac{1}{2}}\tilde{\mathrm{g}}_\mathrm{m}$ can be presented as $\tilde{\mathrm{g}}_\mathrm{m}\gamma_m{}^{-\frac{1}{2}}$ where γ_m is defined

as a formula incorporating Ω and approximation of $\Omega^{-\frac{1}{2}}\tilde{\mathrm{g}}_{\mathrm{m}} \approx \tilde{\mathrm{g}}_{\mathrm{m}}\gamma_m{}^{-\frac{1}{2}}$ is allowed. From this following equation can be obtained.

$$T^2_{Score,m} \approx \frac{N[\tilde{\mathrm{g}}_{\mathrm{M}}^{\mathrm{T}}(\Omega^{-\frac{1}{2}}\tilde{\mathrm{y}}\gamma^{-\frac{1}{2}})]^2}{(\tilde{\mathrm{g}}_{\mathrm{M}}^{\mathrm{T}}\tilde{\mathrm{g}}_{\mathrm{m}})(\gamma^{-\frac{1}{2}}\tilde{\mathrm{y}}^{\mathrm{T}}\Omega^{-\frac{1}{2}})(\Omega^{-\frac{1}{2}}\tilde{\mathrm{y}}\gamma^{-\frac{1}{2}})}$$

And since the $\Omega^{-\frac{1}{2}}\tilde{\mathrm{y}}\gamma^{-\frac{1}{2}}$ does not include any information about the genetic marker, this is defined as $y^{\oplus}$ and the score statistic can be further defined as following.

$$T^2_{Score,m} \approx \frac{N(\tilde{\mathrm{g}}_{\mathrm{M}}^{\mathrm{T}}\, y^{\oplus})^2}{(\tilde{\mathrm{g}}_{\mathrm{M}}^{\mathrm{T}}\tilde{\mathrm{g}}_{\mathrm{m}})(\, y^{\oplus T}\, y^{\oplus})} = T^2_{Gr+,m}$$

By this method, the phenotypes of related samples can be transformed, adjusted for familial relationship, and the adjusted value can be used in a simple linear regression model for unrelated samples [161].

The interaction of gene and personality was evaluated by comparing the beta coefficient of two different groups by Z statistics. When the direction of mean change of health behavior traits by personality groups from the linear trend test was positive, group 1 was defined as upper group of tertiled personality and group 2 was defined as middle and lower group of tertile, and vice versa for the negative trend. The grouping was applied to see the effect of utmost personality score on health behaviors, instead of simply dividing them into two groups by their median value. This test was implemented in the PLINK as ‘gxe’ option.

3. Results

Table 4.1. General Characteristics of health behavior related traits, stratified by gender

	Men		Women		
	n	mean(S.D)	n	mean(S.D)	p-value †
BMI (kg/m2)	1418	24.44(3.02)	2058	23.13(3.28)	<0.0001
DEBQ-RSE	1408	2.08(0.90)	2026	2.58(1.00)	<0.0001
DEBQ-EME	1410	1.32(0.56)	2034	1.56(0.76)	<0.0001
DEBQ-EXE	1402	2.58(0.75)	2015	2.78(0.76)	<0.0001
Smoking Status (%)					<0.0001
Non-smoker		403(28.42)		1868(90.72)	
Ex-smoker		398(28.07)		62(3.01)	
Current smoker		617(43.51)		129(6.27)	
Pack-Year	879	18.82(17.12)	144	6.30(6.15)	<0.0001
FTND	1004	3.38(2.47)	188	2.42(2.31)	<0.0001
Alcohol Drinking Status (%)					<0.0001
Never drinkers		191(13.47)		774(37.57)	
Ex-drinkers		120(8.46)		201(9.76)	
Current drinkers		1107(78.07)		1085(52.67)	
Alcohol Intake (g/week)	1097	178.14(257.64)	1052	52.45(96.61)	<0.0001
AUDIT-C	1194	6.55(3.08)	1247	3.51(2.50)	<0.0001
AUDIT	1189	11.16(7.34)	1242	5.20(5.02)	<0.0001

† significant difference obtained by Student's t-test and chi-squared test
All rounded to the nearest tenth,
Abbreviations: S.D, Standard Deviation; BMI, Body Mass Index; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions;

The general characteristics of targeted health behaviors are displayed in Table 4.1. Despite higher BMI among male participants, all of the DEBQ domains were significantly higher in female participants. There were more current and former smokers among male, and the amount of cigarette smoked (pack-year) and score for FTND was higher for male participants as well.

Similar trends were also seen for alcohol drinking status, average amount of alcohol intake per week, and average score for AUDIT-C and AUDIT. Significant differences were observed between the genders for all of the traits, even for the weak effects due to large size of the sample for some traits.

3.1. Linear association between personality and health behavior traits

Phenotypic correlations between personality traits measured by TCI and health behaviors are shown in Table 4.2. DEBQ-RSE showed resemblance with NS, RD, PE, CO, and ST. DEBQ-EME was correlated with all dimensions of TCI but RD, whereas DEBQ-EXE was correlated with all but PE and had moderate correlation with NS (r=0.278). FTND was correlated with NS, HA, RD, SD, and CO, and correlation estimation was highest for SD (r=-0.174). AUDIT-C was correlated with NS, RD, SD, and ST. AUDIT score was positively correlated with NS and RD, and negatively correlated with SD and CO.

Association between personality traits and health behavior traits were also observed (Table 4.3) and familial correlation, age, sex, education level, and household income were adjusted for this analysis. Multiple testing correction was applied (0.05/42 tests = 0.001) for significant alpha level. DEBQ-RSE was positively associated with PE and ST even after adjusting for potential confounders. DEBQ-EME had positive association with NS, HA, and ST, and negative association with SD and CO. NS explained 5.9% of DEBQ-EME's variance, and SD explained 4.7%. DEBQ-EXE was positively associated with NS, HA, RD and ST, and negatively associated with SD and

CO. NS explained large proportion of DEBQ-EXE's variance (11.2%), and ST explained about 3.9%. FTND had a positive association with NS and negative relationships with SD and CO, each explaining about 0.6~2.4% of the FTND's variance. AUDIT-C was only positively associated with NS. Lastly, AUDIT was positively associated with NS and RD, and negatively associated with SD and CO (p-value not under 0.001). NS explained about 4% of the AUDIT's variance, while other dimensions only explained less than 1%. Overall, NS had strong association with all targeted health behaviors but DEBQ-RSE, and SD and CO also showed strong negative association with DEBQ-EME, EXE, FTND, and AUDIT. ST was significantly associated with all domains of DEBQ.

Table 4.2. Correlation coefficients between Personality (TCI) and Health behavior traits

	DEBQ-RSE	DEBQ-EME	DEBQ-EXE	FTND	AUDIT-C	AUIDT
Novelty Seeking	0.051*	0.231***	0.278***	0.130***	0.112***	0.173***
Harm Avoidance	0.017	0.172***	0.159***	0.107**	-0.039	0.036
Reward Dependency	0.034*	0.033	0.117***	-0.078**	0.089***	0.092***
Persistence	0.079***	-0.035*	0.010	-0.032	0.016	-0.010
Self-Directedness	0.028	-0.208***	-0.168***	-0.174***	-0.063*	-0.135***
Cooperativeness	0.034*	-0.132***	-0.070***	-0.093*	-0.030	-0.078***
Self-Transcendence	0.114***	0.176***	0.201***	-0.013	-0.101***	-0.038

P value: *, <0.05;**, <0.001; ***, <0.0001
All rounded to the nearest hundredth,
Adjusted for age and gender
Abbreviations: TCI, Temperament and Character Inventory; S.D, Standard Deviation; BMI, Body Mass Index; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions

Table 4.3 Beta Coefficient (± standard error) of regression analysis on Health behavior traits and Personality (TCI)

	Novelty Seeking		Harm Avoidance		Reward Dependency		Persistence		Self-Directedness		Cooperativeness		Self-Transcendence	
	Beta ± S.E.	VE	Beta ± S.E.	VE	Beta ± S.E.	VE	Beta ± S.E.	VE	Beta ± S.E.	VE	Beta ± S.E.	VE	Beta ± S.E.	VE
DEBQ-RSE*	0.002±0.001*	0.001	0.001±0.000	0.003	0.001±0.001	0.005	0.002±0.000***	0.002	0.000±0.000	0.000	0.001±0.001	0.002	0.003±0.000***	0.018
DEBQ-EME*	0.006±0.000***	0.059	0.004±0.000**	0.037	0.001±0.001	0.006	-0.001±0.000*	0.001	-0.005±0.000***	0.047	-0.004±0.000**	0.015	0.004±0.000***	0.034
DEBQ-EXE	0.020±0.001***	0.112	0.011±0.001**	0.028	0.010±0.002***	0.034	0.000±0.001	0.001	-0.013±0.001***	0.030	-0.006±0.001**	0.005	0.012±0.001***	0.039
FTND*	0.009±0.002**	0.006	0.004±0.002	0.008	-0.007±0.003*	0.011	-0.001±0.002	0.002	-0.008±0.002***	0.024	-0.008±0.002**	0.008	-0.000±0.002	0.000
AUDIT-C*	0.006±0.001***	0.028	-0.003±0.001*	0.015	0.005±0.002*	0.002	0.002±0.001	0.009	-0.003±0.001*	0.000	-0.002±0.001	0.002	-0.004±0.001*	0.015
AUDIT*	0.011±0.002***	0.040	-0.001±0.002	0.002	0.007±0.002**	0.002	0.001±0.002	0.003	-0.007±0.002***	0.006	-0.005±0.002*	0.008	-0.003±0.002	0.004

P value: *, <0.05;**, <0.001; ***, <0.0001 Dependent variables – health behavior traits
All rounded to the nearest hundredth, *log-transformed after adding a constant 1
Adjusted for age, sex, education, household income, random effect of family adjusted using mixed model
Abbreviations: TCI, Temperament and Character Inventory; VE, Variance Explained; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT-C, The AUDIT alcohol consumption questions**;** AUDIT, The Alcohol Use Disorders Identification Test;

Table 4.4 Average score of Personality (TCI) by tertile groups

	Lower Tertile		Middle Tertile		Upper Tertile	
	n	mean(S.D)	n	mean(S.D)	n	mean(S.D)
Novelty Seeking	1140	17.61(4.51)	1139	27.83(2.55)	1161	39.84(6.01)
Harm Avoidance	1112	25.55(5.37)	1155	36.92(2.59)	1173	48.92(6.22)
Reward Dependency	1114	33.07(4.58)	1168	42.02(1.99)	1149	51.24(4.46)
Persistence	1105	29.97(5.29)	1199	40.95(2.57)	1139	52.58(5.82)
Self-Directedness	1144	34.46(5.90)	1170	46.01(2.60)	1131	57.08(5.06)
Cooperativeness	1089	43.81(5.10)	1183	53.52(2.23)	1169	63.12(4.55)
Self-Transcendence	1152	13.22(4.64)	1101	24.25(2.86)	1187	38.04(6.57)

All rounded to the nearest hundredth,
Abbreviations: TCI, Temperament and Character Inventory; S.D, Standard Deviation;

All personality scores were ranked, and then were divided into three groups by their tertile. The average scores of TCI of each tertile are shown in Table 4.4. By these tertiles, average scores of each health behavior traits were compared and their linear trend was tested (Table 4.5 and 4.6). The results from this analysis were similar with the linear regression results. DEBQ-RSE showed positive linear trend by PE and ST tertiles. For DEBQ-EME, NS, HA, and ST showed positive linear trend, and average scores of DEBQ-EME decreased by SD and CO tertiles. DEBQ-EXE exhibited significant linear trend for all personality dimensions except for PE. Average scores of FTND was decreased by tertiles of SD. For AUDIT-C and AUDIT, positive linear trend was observed for NS and RD. ST only showed significant negative linear trend for AUDIT-C, and for ADUIT, average scores was decreased by SD and CO tertiles.

Scores of FTND and seven dimensions of TCI were compared between successful tobacco quitters and current smokers (Table 4.7). Average FTND score for continued smoker was 3.63, whereas average score for individuals who stopped smoking was 2.74 (t-test p-value < 0.0001). Also NS score was significantly higher for current smokers, and average scores of SD and ST was higher for individuals who were successful in smoking cessation.

Table 4.5. Mean values of health behavior trait scores by tertiles of personality (TCI)

		Lower Tertile	Middle Tertile	Upper Tertile	
	Tertiled score	mean(S.D)	mean(S.D)	mean(S.D)	P-value ǂ
DEBQ-RSE	NS	2.36(1.02)	2.36(0.95)	2.40(1.00)	0.06
	HA	2.29(0.99)	2.42(0.99)	2.41(0.99)	0.49
	RD	2.31(1.00)	2.37(1.00)	2.44(0.98)	0.15
	PE	2.31(0.97)	2.39(0.98)	2.42(1.02)	<0.0001
	SD	2.39(1.02)	2.33(0.96)	2.41(1.00)	0.21
	CO	2.32(0.97)	2.39(1.00)	2.41(1.01)	0.16
	ST	2.25(0.98)	2.32(0.95)	2.54(1.03)	<0.0001
DEBQ-EME	NS	1.30(0.54)	1.42(0.63)	1.66(0.84)	<0.0001
	HA	1.32(0.57)	1.46(0.70)	1.60(0.78)	<0.0001
	RD	1.39(0.63)	1.47(0.70)	1.53(0.75)	0.03
	PE	1.48(0.71)	1.46(0.70)	1.44(0.67)	0.26
	SD	1.63(0.81)	1.44(0.68)	1.32(0.54)	<0.0001
	CO	1.54(0.76)	1.48(0.70)	1.37(0.60)	<0.0001
	ST	1.33(0.56)	1.44(0.67)	1.61(0.80)	<0.0001
DEBQ-EXE	NS	2.42(0.74)	2.70(0.73)	2.98(0.72)	<0.0001
	HA	2.56(0.77)	2.69(0.74)	2.83(0.76)	<0.0001
	RD	2.55(0.77)	2.69(0.76)	2.85(0.74)	<0.0001
	PE	2.64(0.81)	2.74(0.75)	2.70(0.73)	0.50
	SD	2.85(0.77)	2.69(0.75)	2.55(0.74)	<0.0001
	CO	2.79(0.78)	2.66(0.76)	2.65(0.75)	<0.0001
	ST	2.54(0.77)	2.68(0.76)	2.87(0.73)	<0.0001

ǂ p-value for linear trend, adjusted for age and sex
All rounded to the nearest tenth,
Abbreviations: TCI, Temperament and Character Inventory; S.D, Standard Deviation; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence

Table 4.6. Mean values of health behavior trait scores by tertiles of personality (TCI), continued

	Tertiled score	Lower Tertile mean(S.D)	Middle Tertile mean(S.D)	Upper Tertile mean(S.D)	P-value ǂ
FTND	NS	3.04(2.35)	3.12(2.42)	3.40(2.56)	0.00
	HA	3.00(2.33)	3.30(2.48)	3.46(2.60)	0.00
	RD	3.53(2.49)	3.14(2.47)	2.97(2.43)	0.01
	PE	3.39(2.45)	3.17(2.42)	3.17(2.53)	0.18
	SD	3.73(2.58)	3.11(2.44)	2.84(2.31)	<0.0001
	CO	3.50(2.51)	3.16(2.46)	3.00(2.43)	0.00
	ST	3.25(2.42)	3.30(2.48)	3.12(2.52)	0.55
AUDIT-C	NS	4.40(3.16)	4.96(3.09)	5.47(3.21)	<0.0001
	HA	5.41(3.20)	4.97(3.10)	4.61(3.20)	0.08
	RD	4.69(3.12)	5.18(3.20)	5.09(3.22)	<0.0001
	PE	4.75(3.23)	4.98(3.17)	5.23(3.13)	0.86
	SD	5.02(3.22)	5.10(3.20)	4.86(3.13)	0.01
	CO	5.30(3.25)	4.91(3.12)	4.78(3.18)	0.02
	ST	5.36(3.24)	5.14(3.15)	4.42(3.08)	<0.0001
AUDIT	NS	6.50(6.09)	7.88(6.55)	9.50(7.47)	<0.0001
	HA	8.38(6.72)	8.07(6.82)	7.86(7.19)	0.17
	RD	7.47(6.60)	8.49(7.07)	8.34(7.06)	<0.0001
	PE	7.75(7.09)	8.13(6.94)	8.40(6.71)	0.70
	SD	8.70(7.45)	8.27(6.93)	7.35(6.26)	<0.0001
	CO	9.02(7.49)	7.94(6.69)	7.36(6.47)	<0.0001
	ST	8.50(7.00)	8.38(6.85)	7.35(6.72)	0.01

ǂ p-value for linear trend, adjusted for age and sex
All rounded to the nearest tenth
Abbreviations: TCI, Temperament and Character Inventory; S.D, Standard Deviation; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence

Table 4.7. Comparison of Personality Scores (TCI) and FTND between successful smoking quitters and current smokers

	Stopped Smoking (n=541)	Continued Smoking (n=665)	
	mean(S.D)	mean(S.D)	p value †
FTND	2.74(2.56)	3.63(2.33)	<0.0001
NS	29.16(9.38)	32.26(9.91)	<0.0001
HA	35.10(10.70)	35.82(10.57)	0.24
RD	41.47(8.15)	42.04(7.71)	0.22
PE	42.76(10.10)	42.58(10.35)	0.77
SD	47.62(10.23)	44.31(10.33)	<0.0001
CO	53.29(8.84)	52.48(8.44)	0.11
ST	24.85(11.27)	22.97(10.15)	0.00

† significant difference obtained by Student's t-test
Abbreviations: TCI, Temperament and Character Inventory; S.D, Standard Deviation; FTND, Fagerstrom Test for Nicotine Dependence; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence
All rounded to the nearest tenth

3.2. Comparison of groups divided according to combination of personality dimensions of NS, SD, and CO

Table 4.8 displays mean value of traits by four different groups, where individuals are assigned by their NS and SD level. Group 1, which was hypothesized to have lowest average scores of health behavior traits, had significantly lower mean scores when compared to group 4 and group 2, 3, and 4 combined for DEBQ-EME, EXE, FTND, AUDIT-C, and AUDIT. Group 4 also had highest mean value when compared to rest of the groups in these traits. Proportion of the successful cigarette quitters was also lowest in group 4 (33.59%), while group 1's proportion was 55.59%. Differences in

BMI level, amount of smoking in pack-year, and alcohol intake amount were also observed in these groups, but they were not as significant as the differences in two of the eating behavior scores and dependency scores. Similar trend was observed for groups divided by levels of NS and CO (Table 4.9). Comparisons for groups divided according to individual's score of SD and CO are shown in table 4.10. Group 4, characterized by low SD and low CO level, had highest trait averages when compared with group 1 for DEBQ-EME, EXE, FTND, and AUDIT. However AUDIT-C did not show statistically significant differences among the groups. Also BMI was not different among groups even when group 1 and group 4 were compared, which is not constant with the outcomes of emotional and external eating behaviors. Proportion of successful smoking quitters and average pack-year smoked was significantly different among groups, but no difference was observed for amount of alcohol intake.

In order to see if the targeted health behavior trait scores that are used in this study well represent corresponding problematic health behaviors, their linear trend was analyzed (Table 4.11). Mean level of BMI increased by tertile group of all DEBQ domains (p-value=<0.0001 for restrained and emotional eating, p-value=0.007 for external eating). Amount of cigarette smoking represented by pack-year also showed increasing linear trend by the tertile of FTND (p-value=<0.0001), and average of amount of alcohol intake (g per week) also showed increasing trend by the tertiles grouped by AUDIT-C and AUDIT scores (p-value=<0.0001).

Table 4.8. Comparison and contrast of means between groups divided by level of Novelty Seeking and Self-Directedness

	Group 1 Low NS High SD		Group 2 Low NS Low SD		Group 3 High NS High SD		Group 4 High NS Low SD		p-value*	1 vs 4	1,2,3 vs 4	1 vs 2,3,4
	N	Mean (S.D.)	N	Mean (S.D.)	N	Mean (S.D.)	N	Mean (S.D.)				
DEBQ-RSE	967	2.35(0.99)	682	2.35(1.06)	770	2.39(0.95)	957	2.40(1.01)	0.23	0.35	0.27	0.69
DEBQ-EME	957	1.27(0.50)	685	1.41(0.63)	771	1.46(0.67)	955	1.71(0.86)	<0.0001	<0.0001	<0.0001	<0.0001
DEBQ-EXE	960	2.42(0.72)	679	2.57(0.74)	771	2.82(0.73)	948	2.98(0.73)	<0.0001	<0.0001	<0.0001	<0.0001
FTND	282	2.80(2.26)	176	3.55(2.56)	337	3.11(2.52)	381	3.50(2.49)	<0.0001	<0.0001	0.00	<0.0001
AUDIT-C	624	4.62(3.05)	442	4.38(3.16)	601	5.40(3.20)	741	5.36(3.20)	<0.0001	<0.0001	<0.0001	0.01
AUDIT	621	6.75(6.02)	441	6.91(6.52)	598	8.74(6.78)	738	9.48(7.58)	<0.0001	<0.0001	<0.0001	<0.0001
Successful Smoking Cessation (%)		159(55.59)		84(46.93)		159(46.63)		129(33.59)	<0.0001t			
BMI	980	23.63(3.07)	691	23.61(3.24)	781	23.78(3.35)	962	23.63(23.63)	0.02	0.08	0.31	0.07
Pack-Year	244	17.24(13.86)	148	20.25(17.23)	300	14.67(14.34)	317	16.55(15.22)	0.00	0.00	0.03	0.00
g/week	234	87.70(126.85)	380	88.53(132.45)	533	117.51(144.25)	662	121.97(159.37)	0.00	0.00	0.00	0.01

* adjusted for age, gender, and random effect of family adjusted using mixed model

Abbreviations: S.D, Standard Deviation; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions; NS, Novelty Seeking; SD, Self-Directedness;

t obtained by chi-squared test

All rounded to the nearest tenth

Table 4.9. Comparison and contrast of means between groups divided by level of Novelty Seeking and Cooperativeness

	Group 1 Low NS High CO		Group 2 Low NS Low CO		Group 3 High NS High CO		Group 4 High NS Low CO		p-value*	1 vs 4	1,2,3 vs 4	1 vs 2,3,4
	N	Mean (S.D.)	N	Mean (S.D.)	N	Mean (S.D.)	N	Mean (S.D.)				
DEBQ-RSE	923	2.37(1.02)	730	2.33(0.98)	801	2.42(0.98)	922	2.36(0.98)	0.26	0.58	0.69	0.61
DEBQ-EME	931	1.28(0.51)	732	1.39(0.61)	802	1.53(0.74)	920	1.65(0.82)	<0.0001	<0.0001	<0.0001	<0.0001
DEBQ-EXE	921	2.46(0.71)	723	2.51(0.76)	797	2.86(0.73)	917	2.95(0.74)	<0.0001	<0.0001	<0.0001	<0.0001
FTND	249	2.92(2.33)	211	3.29(2.47)	308	3.26(2.52)	406	3.36(2.52)	0.03	0.00	0.03	0.07
AUDIT-C	562	4.44(3.08)	503	4.62(3.12)	583	5.36(3.21)	753	5.41(3.20)	<0.0001	<0.0001	0.01	0.00
AUDIT	561	6.53(6.04)	500	7.14(6.44)	582	8.77(6.83)	748	9.47(7.54)	<0.0001	<0.0001	<0.0001	<0.0001
Successful Smoking Cessation (%)		136(53.75)		110(51.40)		132(42.31)		156(38.14)	0.00 t			
BMI	939	23.53(3.11)	737	23.71(3.17)	808	23.69(3.33)	931	23.70(3.34)	0.01	0.01	0.06	0.01
Pack-Year	209	17.61(14.73)	183	19.35(15.81)	270	15.37(14.62)	345	15.84(15.03)	0.17	0.05	0.38	0.03
g/week	485	88.57(137.23)	428	89.64(125.13)	514	118.81(149.43)	675	121.20(155.80)	0.01	0.00	0.05	0.01

* adjusted for age, gender, and random effect of family adjusted using mixed model

Abbreviations: S.D, Standard Deviation; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions; NS, Novelty Seeking; CO, Cooperativeness;

t obtained by chi-squared test

All rounded to the nearest tenth

Table 4.10. Comparison and contrast of means between groups divided by level of Self-Directedness and Cooperativeness

	Group 1		Group 2		Group 3		Group 4					
	High SD High CO		High SD Low CO		Low SD High CO		Low SD Low CO		p-value*	1 vs 4	1,2,3 vs 4	1 vs 2,3,4
	N	Mean (S.D.)	N	Mean (S.D.)	N	Mean (S.D.)	N	Mean (S.D.)				
DEBQ-RSE	1056	2.37(0.98)	682	2.37(0.98)	672	2.45(1.04)	971	2.33(0.98)	0.09	0.22	0.02	0.71
DEBQ-EME	1061	1.31(0.56)	688	1.41(0.62)	677	1.52(0.72)	967	1.62(0.81)	<0.0001	<0.0001	<0.0001	<0.0001
DEBQ-EXE	1054	2.58(0.74)	680	2.62(0.77)	670	2.75(0.75)	961	2.84(0.77)	<0.0001	<0.0001	<0.0001	<0.0001
FTND	349	2.98(2.37)	271	3.00(2.50)	211	3.33(2.56)	349	3.61(2.47)	0.00	0.00	0.00	0.01
AUDIT-C	704	4.91(3.15)	523	5.14(3.15)	444	4.92(3.24)	737	5.07(3.22)	0.09	0.03	0.29	0.02
AUDIT	703	7.41(6.22)	518	8.14(6.81)	443	8.09(7.03)	734	8.86(7.55)	<0.0001	<0.0001	0.0001	<0.0001
Successful Smoking Cessation (%)		189(53.39)		133(48.54)		80(37.38)		135(38.35)	<0.0001 t			
BMI	1072	23.61(3.20)	692	23.83(3.19)	680	23.61(3.26)	977	23.62(3.31)	0.69	0.82	0.82	0.55
Pack-Year	304	15.15(13.02)	242	17.03(16.02)	179	18.55(17.54)	290	17.25(14.84)	0.00	0.00	0.07	0.00
g/week	611	98.52(134.38)	454	107.95(139.50)	389	111.03(153.87)	652	110.45(150.12)	0.05	0.08	0.90	0.01

* adjusted for age, gender, and random effect of family adjusted using mixed model

Abbreviations: S.D, Standard Deviation; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions; SD, Self-Directedness; CO, Cooperativeness;

t obtained by chi-squared test

All rounded to the nearest tenth

Table 4.11. Mean values of BMI, Pack-Year, and Alcohol intake (g/week) by tertiles of corresponding health behavior trait scores

		Lower Tertile		Middle Tertile		Upper Tertile		p value ǂ
	Tertiled score	n	mean(S.D)	n	mean(S.D)	n	mean(S.D)	
BMI (kg/m2)	DEBQ-RSE	1177	22.79(3.11)	1090	24.06(3.24)	1164	24.17(3.20)	<0.0001
	DEBQ-EME	1194	23.61(3.12)	1164	23.53(3.15)	1083	23.86(3.47)	<0.0001
	DEBQ-EXE	1116	23.79(3.26)	1198	23.79(3.18)	1100	23.43(3.28)	0.01
Pack-Year	FTND	285	8.45(9.00)	422	15.12(10.96)	302	25.97(17.59)	<0.0001
Alcohol Intake (g/week)	AUDIT-C	690	16.52(21.81)	671	58.20(57.60)	776	237.35(195.60)	<0.0001
	AUDIT	572	13.65(14.57)	738	55.96(59.30)	819	224.94(195.99)	<0.0001

ǂ p-value for linear trend, adjusted for age and sex

All rounded to the nearest tenth,

Abbreviations: S.D, Standard Deviation; BMI, Body Mass Index; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions;

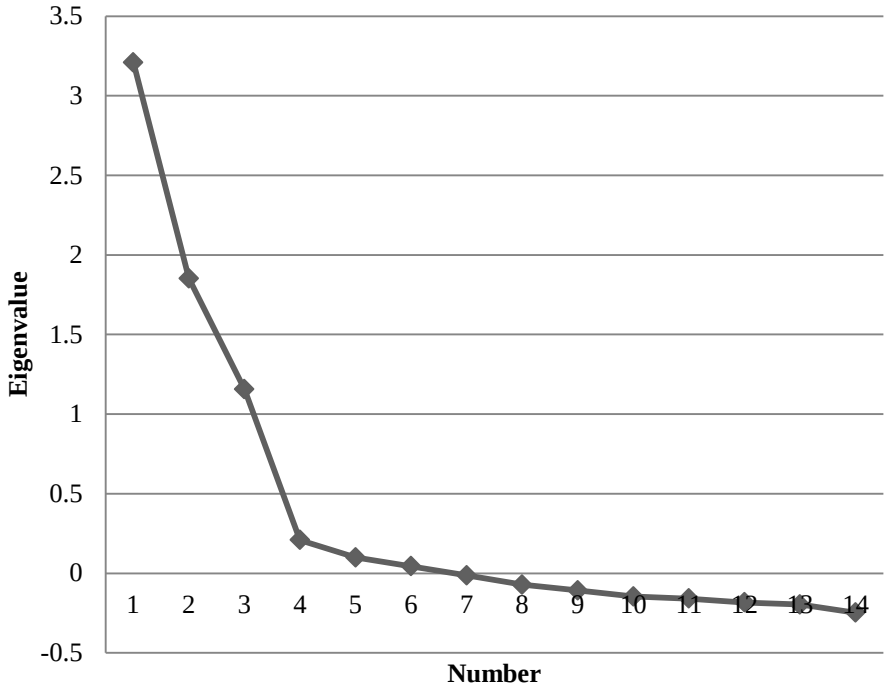


Figure 4.1.Scree plot of eigenvalues from principal axis analysis

Table 4.12. The Oblimin-rotated factor pattern of sub-dimensions of Novelty Seeking, Self-directedness, and Cooperativeness

	Factor1	Factor2	Factor3
	Determinedness	Vulnerability	Fondness
SD5: Enlightened second nature	**0.74**	-0.16	0.04
SD2: Purposefulness	**0.68**	0.06	0.04
SD4: Self-acceptance	**0.67**	-0.10	-0.14
SD1: Responsibility	**0.65**	-0.12	-0.12
SD3: Resourcefulness	**0.63**	0.28	0.25
NS2: Impulsiveness	-0.17	**0.66**	0.05
NS4: Disorderliness	-0.05	**0.63**	-0.20
NS1: Exploratory excitability	0.22	**0.59**	0.24
NS3: Extravagance	-0.13	**0.53**	-0.05
CO1: Social acceptance	0.18	**-0.38**	0.19
CO3: Helpfulness	-0.03	0.20	**0.72**
CO2: Empathy	0.01	0.13	**0.67**
CO5: Principles	-0.01	-0.21	**0.57**
CO4: Compassion	-0.01	-0.22	**0.49**
Proportion of Variance Explained	0.59	0.34	0.21

Abbreviations: NS, Novelty Seeking SD, Self-Directedness; CO, Cooperativeness; In Bold if loading higher than 0.30; All rounded to the nearest tenth

Table 4.13. Correlation coefficients between Factors and Health behavior traits

	Factor1	Factor2	Factor3	DEBQ-RSE	DEBQ-EME	DEBQ-EXE	FTND	AUDIT-C	AUDIT
Factor1	1	-0.29***	0.36***	0.02	-0.23***	-0.19***	-0.18***	-0.06*	-0.14***
Factor2	-0.29***	1	-0.01	0.07***	0.24***	0.29***	0.13***	0.10***	0.17***
Factor3	0.36***	-0.01	1	0.08***	-0.08***	-0.01	-0.08*	-0.03	-0.06*

P value: *, <0.05;**, <0.001; ***, <0.0001
All rounded to the nearest tenth,
Adjusted for age and gender
Abbreviations: S.D, Standard Deviation; BMI, Body Mass Index; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions;

Table 4.14. Association between Health behavior traits and personality patterns

	Factor 1 Determinedness		Factor 2 Vulnerability		Factor 3 Fondness			
	Beta±S.E.	P-value	Beta±S.E.	P-value	Beta±S.E.	P-value	R^2	V.E.
DEBQ-RSE*	0.01±0.01	0.13	0.03±0.01	<0.0001	0.02±0.01	0.0007	0.09	0.01
DEBQ-EME*	-0.04±0.00	<0.0001	0.06±0.00	<0.0001	-0.01±0.00	0.11	0.15	0.10
DEBQ-EXE	-0.10±0.01	<0.0001	0.23±0.02	<0.0001	0.03±0.01	0.03	0.21	0.14
FTND*	-0.10±0.03	0.0001	0.05±0.03	0.04	-0.03±0.03	0.25	0.06	0.03
AUDIT-C*	-0.01±0.01	0.34	0.06±0.01	<0.0001	-0.01±0.01	0.49	0.21	0.03
AUDIT*	-0.05±0.02	0.01	0.12±0.02	<0.0001	-0.02±0.02	0.21	0.22	0.04

Dependent variables – health behavior traits
Adjusted for age, sex
All rounded to the nearest tenth,
*log-transformed after adding a constant 1
Abbreviations: S.E, Standard Error; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption question**;** VE, Variance Explained

3.3. Principal Axis Analysis and association with health behaviors

Figure 4.1 shows the scree plot of eigenvalues of each factors retained from the factor analysis by PA method. Factor 1~3 had eigenvalue above 1, exceeding the criteria for amount of data variance explained. Factor 1 had eigenvalue of 3.21 with the represented proportion of variation of 0.59. Factor 2 had eigenvalue of 1.85 representing 0.34 of the variation, and factor 3 had eigenvalue of 1.16 explaining 0.21 of the variation. Factor 1 (Determinedness) is characterized by high factor pattern coefficient of SD subdomains (0.63~0.74), low coefficient of CO subdomains (-0.03~0.18), and even lower factor loadings for subdomains of NS (-0.17~0.22) (Table 4.12). Factor 2 (Vulnerability) was characterized for high coefficients for NS domains (0.53~0.66), and low loading for SD (-0.16~0.28), and CO (-0.38~0.20). Factor 3 (Fondness) had high loading for CO and low loading for SD and NS.

Correlation between the factors and health behavior traits are shown in Table 4.13. All three factors were correlated to each other, and Vulnerability was significantly correlated with all of the health behavior traits. Determinedness was not correlated with restrained eating, and Fondness was positively correlated with DEBQ-RSE and negatively correlated with DEBQ-EME, FTND, and AUDIT. From the multiple regression models incorporating all three factors, Vulnerability was shown to have relatively higher effect sizes on health behaviors when controlled for other remaining factors. Vulnerability was significantly associated with all of the health behaviors when association

was tested adjusting for age, gender, education and household income level, and familial correlation, explaining 0~13% if the variances in risky health behaviors (Table 4.14).

Table 4.15. Association between Health behavior traits and Vulnerability

	Factor 2 Vulnerability		
	Beta±S.E.	P-value	V. E by Vulnerability
DEBQ-RSE*	0.03±0.01	<0.0001	0.00
DEBQ-EME*	0.07±0.00	<0.0001	0.07
DEBQ-EXE	0.25±0.02	<0.0001	0.13
FTND*	0.10±0.02	<0.0001	0.01
AUDIT-C*	0.07±0.01	<0.0001	0.02
AUDIT*	0.14±0.02	<0.0001	0.04

All rounded to the nearest tenth, *log-transformed after adding a constant 1

Adjusted for age, sex, education, household income, random effect of family adjusted by mixed model

Abbreviations: S.E, Standard Error; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions; VE, Variance Explained

Vulnerability - principal-axis factorization of subdomains of NS, SD, and CO. Characterized by high NS and low SD and CO loadings

Figure 4.2 Completed Partially Directed Acyclic Graph (CPDAG) of Vulnerability and risky health behaviors with covariates

Vulnerability - principal-axis factorization of subdomains of NS, SD, and CO. Characterized by high NS and low SD and CO loadings

When CPDAG was drawn including the covariates, Vulnerability showed directed path towards all of the risky health behaviors investigated in this study, which were not trough covariates such as BMI, income, and education level (Figure 4.2). However these covariates also showed effect on health behaviors via separate path. For DEBQ-RSE, Vulnerability's effect was small (0.08) compared to its effect on DEBQ-EME (0.18). On the other hand, the relationship between DEBQ-EXE and Vulnerability was bidirectional, which is caused due to uncertainty in the observed data. The causal effect

coefficient of Vulnerability on FTND was 0.42, where education and income level had negative effect on FTND (-0.55 and -0.40, respectively). For the DAG for AUDIT, Vulnerability had stronger effect than other health behaviors (1.24), and income level was also a parent of AUDIT (-0.77). Effect coefficient for Vulnerability on AUDIT-C was 0.33, and education also had strong negative effect on AUDIT-C (-0.52).

3.4. Prediction model using Vulnerability

Adding Vulnerability to age-only prediction model improved the model for DEBQ-EME and EXE of eating behaviors (Figure 4.3). AUC of full model for prediction of EME was 0.69 (95% CI, 0.64-0.74), and 0.72 (0.68-0.77) for EXE in males in validation set. For females, AUC of Vulnerability and age model for prediction of EME was 0.68(0.64-0.72), and 0.67(0.63-0.71) for EXE. Vulnerability did not well predict RSE nor improved the model in prediction for both genders.

In Figure 4.4, adding Vulnerability to model for prediction of FTND for males was slightly improved (IDI=0.02(0.01-0.03)), but AUC derived from the validation set was not high (0.57(0.52-0.63)). Prediction of FTND for female was not also successful using Vulnerability. For AUDIT, slight improvement of model was observed for both genders. When interaction by gender was considered in the prediction model with age, sex, and Vulnerability, it did not significantly improve any of the model's prediction.

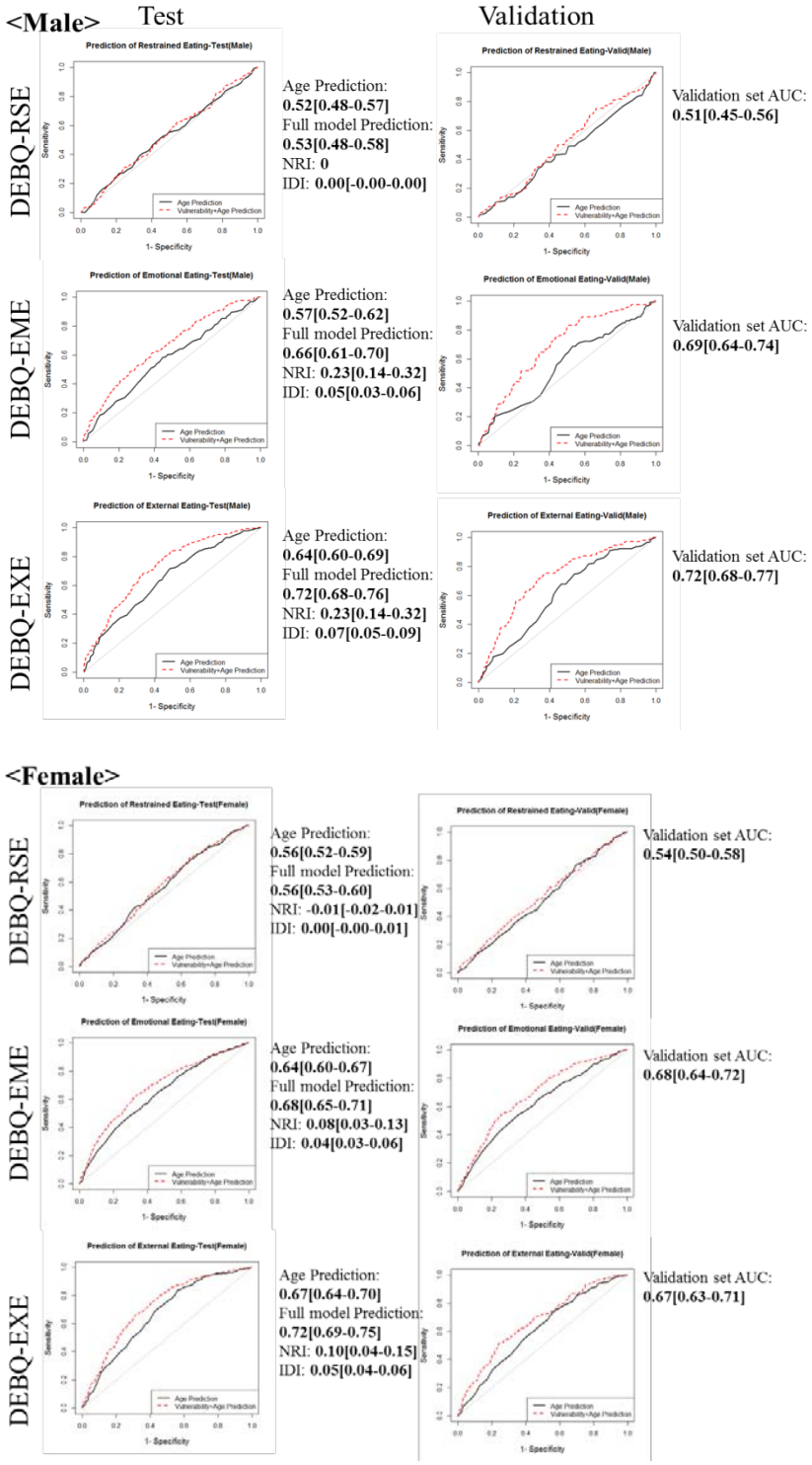


Figure 4.3. Prediction Model of eating behaviors using age and Vulnerability, stratified by gender (Male: Test set n=822, Validation set n=568; Female: Test set n=1171, Validation set n=811) Vulnerability - principal-axis factorization of subdomains of NS, SD, and CO. Characterized by high NS and low SD and CO loadings, All rounded to the nearest tenth

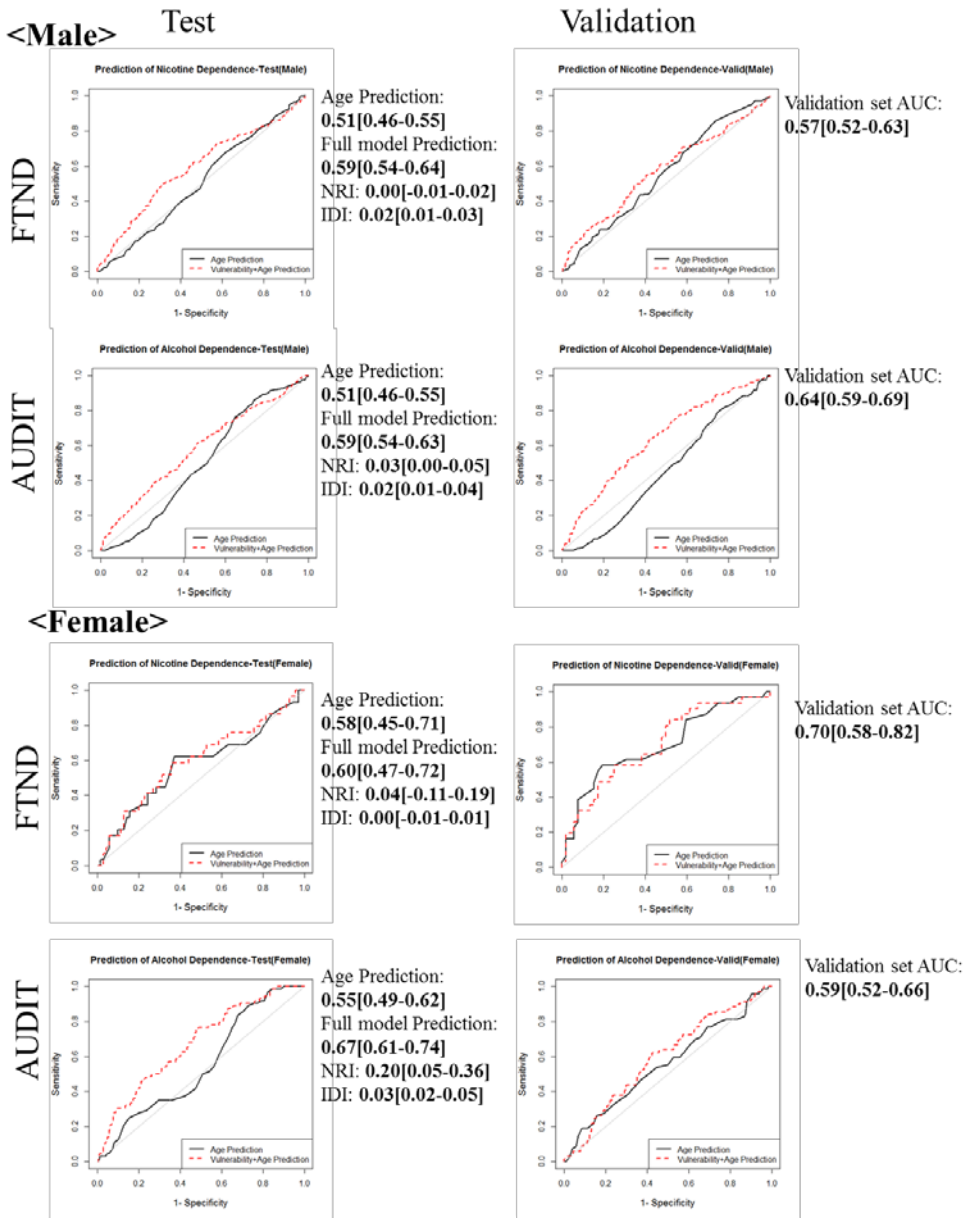


Figure 4.4. Prediction Model of dependency traits using age and Vulnerability, stratified by gender (FTND Male: Test set n=568, Validation set n=421; Female: Test set n=99, Validation set n=83; AUDIT Male: Test set n=699, Validation set n=474; Female: Test set n=699, Validation set n=513) Vulnerability - principal-axis factorization of subdomains of NS, SD, and CO. Characterized by high NS and low SD and CO loadings, All rounded to the nearest tenth

3.5. Gene-by-personality (GxP) interaction analysis

Gene-by-personality (GxP) interaction was tested for those genetic variants that were reported to be related to neurotransmitter activities or psychosocial traits. For each health behavior traits, top 5 genetic variants that had interaction with TCI dimensions are listed in Table 4.16. Among these variants, there were 3 genetic loci that showed significance after FDR correction. For DEBQ-EME, Synaptosomal-Associated Protein, 25kDa (*SNAP25*, rs3630350) and ST showed significant interacting effect (p-value=2.92E-5). Several genetic variants in Enah/Vasp-like (*EVL*) gene and SD showed significant interaction for scores of DEBQ-EXE with lowest p-value of 9.40E-6. For FTND, two SNPs (rs1006737, rs2159100) of Calcium Channel, Voltage-Dependent, L Type, Alpha 1C Subunit (*CACNA1C*) had significant interaction with CO (p-value = 4.12E-5). The significant results from GxP analysis were plotted in Figure 4.2. The directions of trends of average score by genotypes were different for different personality groups. Because there were only 4 individuals with A/A genotype for rs1006737, dominant model was used for the plotting.

Q-Q plot of GxP p-values for these traits are shown in Figure 4.6. Lambda (λ) for DEBQ-EME and ST interaction results was 1.24, 0.97 for DEBQ-EXE and SD, and 0.84 for FTND and CO. Because inflation factor for DEBQ-EME and ST was higher than 1.05, the p-values were adjusted by genomic control. The p-value before the genomic control adjustment of top SNP rs363050 (*SNAP25*) was 2.92E-05, and after the adjustment, the p-value was corrected to 1.79E-4. The corrected p-value was still significant after the

multiple comparison FDR adjustment (p=0.034).

The GxP effect was also examined for 3 SNPs that were genome-wide significantly or suggestively associated with personality in Chapter 3. There were several combinations that had p-value under 0.05, but none of the results exceeded the significance level after the multiple comparison correction (Table 4.17). The plots of these results are shown in Figure 4.7. There were only 5 individuals with T/T genotypes for rs12926331, who had measures for FTND available, and dominant model was used.

Table 4.16. Top 5 Gene-by-Personality interaction among neuropsychological candidate genes by health behavior traits

	TCI-Trait	CHR	SNP	Gene	G1-n	G1-BETA(S.E)	G2-n	G2-BETA(S.E)	P_GXE	Related Phenotype
DEBQ-RSE	NS	12	rs2272495	*APPL2*	1873	-0.031(0.039)	939	0.169(0.054)	0.003	Autism
	CO	4	rs1801260	*CLOCK*	1859	-0.141(0.053)	951	0.125(0.076)	0.004	ADHD, Sleeping Time
	HA	11	rs668387	*SORL1*	1846	-0.051(0.035)	937	0.118(0.049)	0.005	Alzheimer's Disease
	HA	11	rs641120	*SORL1*	1785	-0.060(0.035)	906	0.109(0.049)	0.005	
	CO	22	rs6269	*COMT*	1812	0.048(0.036)	928	-0.131(0.054)	0.006	Hyperactivity, Obsessive-Compulsive Disorder,Schizophrenia, Cocaine dependence, Memory
DEBQ-EME	ST	20	rs363050	*SNAP25*	1814	-0.020(0.026)	963	0.192(0.044)	**2.92E-05**	Intelligence (IQ:non-verbal), ADHD
	ST	12	rs7305115	*TPH2*	1822	0.042(0.022)	971	-0.098(0.037)	0.001	Obsessive compulsive disorder, Heroin addiction, ADHD, Anxiety, Bipolar disorder
	ST	12	rs7963720	*TPH2*	1835	0.040(0.022)	977	-0.095(0.037)	0.002	
	ST	12	rs4570625	*TPH2*	1801	-0.034(0.022)	967	0.092(0.037)	0.003	
	CO	11	rs2373115	*GAB2*	880	-0.080(0.037)	1910	0.050(0.023)	0.003	Alzheimer's Disease
DEBQ-EXE	SD	14	rs11160570	*EVL*	904	-0.217(0.049)	1845	0.045(0.033)	**9.40E-06**	Paranoia(components of hostility)
	SD	14	rs7159195	*EVL*	905	-0.194(0.050)	1855	0.051(0.032)	**4.43E-05**	
	SD	14	rs7158754	*EVL*	905	-0.194(0.050)	1855	0.051(0.032)	**4.43E-05**	
	SD	14	rs2181102	*EVL*	906	-0.190(0.050)	1855	0.051(0.032)	**5.15E-05**	
	SD	14	rs3783337	*EVL*	913	-0.185(0.049)	1862	0.048(0.032)	**6.58E-05**	

FTND	CO	12	rs1006737	*CACNA1C*	357	1.352(0.438)	615	-0.927(0.342)	**4.12E-05**	Bipolar disorder
	CO	12	rs2159100	*CACNA1C*	357	1.352(0.438)	615	-0.927(0.342)	**4.12E-05**	
	RD	11	rs6276	*DRD2*	335	-0.483(0.196)	627	0.301(0.145)	0.001	Schizophrenia, Alcoholism, Nicotine dependence
	RD	4	rs356219	*SNCA*	337	0.651(0.200)	637	-0.118(0.145)	0.002	Parkinson's Disease
	RD	11	rs1800497	*ANKK1*	333	-0.383(0.206)	632	0.390(0.148)	0.002	Obsessive-Compulsive Disorder, Addictive behaviors, Alcoholism, Intelligence (learning from errors)
AUDIT-C	NS	22	rs6269	*COMT*	1192	0.189(0.131)	735	-0.585(0.171)	0.000	*
	NS	22	rs737865	*COMT*	1218	0.268(0.134)	745	-0.519(0.183)	0.001	*
	HA	7	rs7782965	*CHRM2*	615	0.473(0.178)	1261	-0.272(0.120)	0.001	*
	PE	22	rs165599	*COMT*	1262	-0.188(0.122)	683	0.459(0.157)	0.001	*
	RD	11	rs211105	*TPH1*	1281	0.312(0.170)	682	-0.620(0.248)	0.002	Schizophrenia, Heroin addiction, Depression
AUDIT	HA	7	rs7782965	*CHRM2*	612	1.260(0.385)	1256	-0.452(0.271)	0.000	Intelligence / IQ, Depression
	PE	22	rs165599	*COMT*	1258	-0.593(0.274)	679	1.006(0.348)	0.000	*
	HA	7	rs2350780	*CHRM2*	627	1.185(0.373)	1286	-0.393(0.260)	0.001	*
	NS	22	rs165599	*COMT*	1203	-0.583(0.256)	736	0.934(0.371)	0.001	*
	HA	6	rs2619522	*DTNBP1*	641	1.936(0.673)	1314	-0.612(0.477)	0.002	Intelligence / IQ (cognitive abilities, attention, memory), Schizophrenia

* Has been stated in the table previously, All rounded to the nearest hundredth
Adjusted for age, sex, and family correlation, P-value below false discovery rate 0.05 are bolded
Abbreviations: TCI, Temperament and Character Inventory; S.E, Standard Error; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; AUDIT, The Alcohol Use Disorders Identification Test; AUDIT-C, The AUDIT alcohol consumption questions ; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence; ADHD Attention Deficit Hyperactivity Disorder

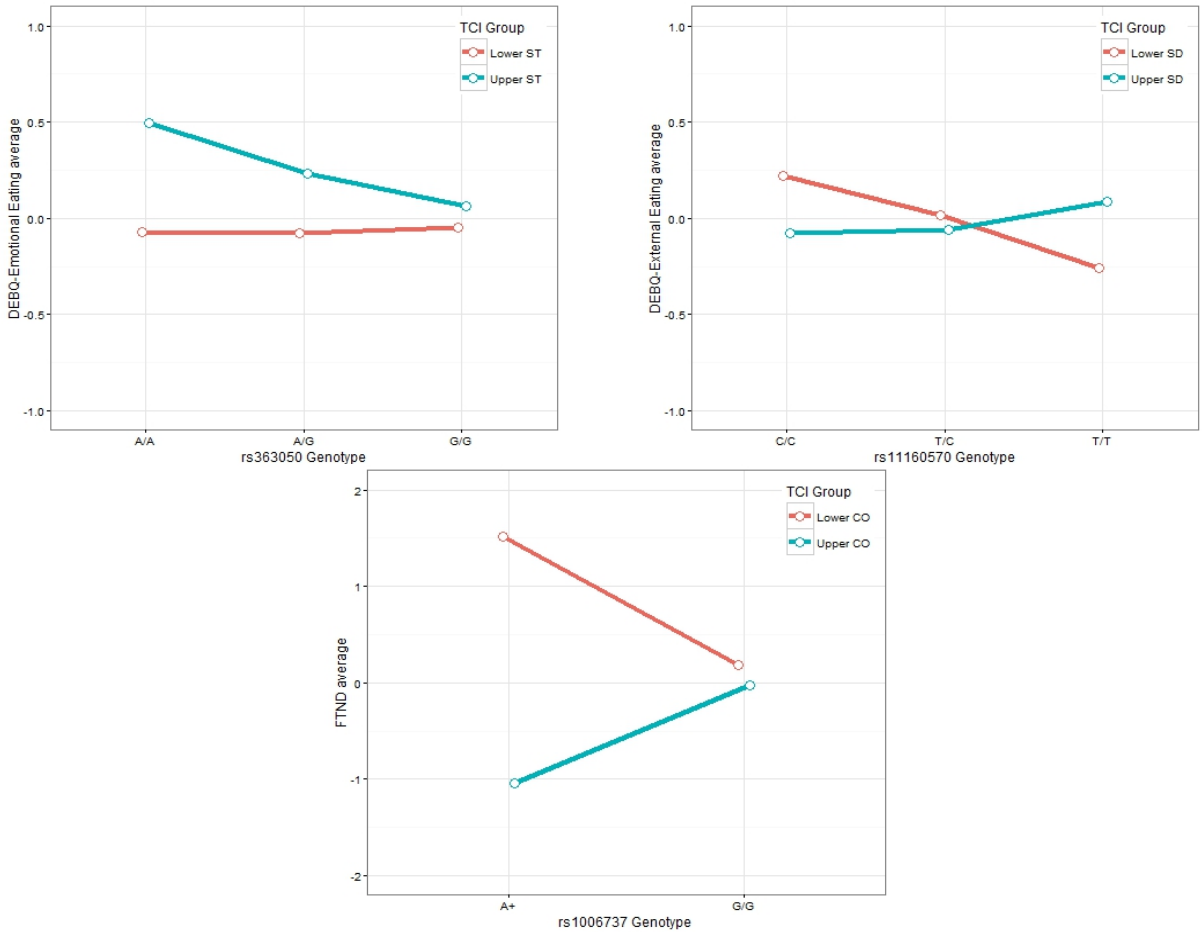
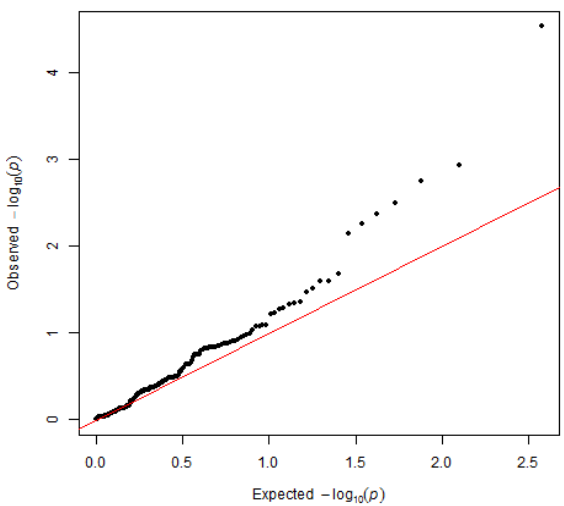
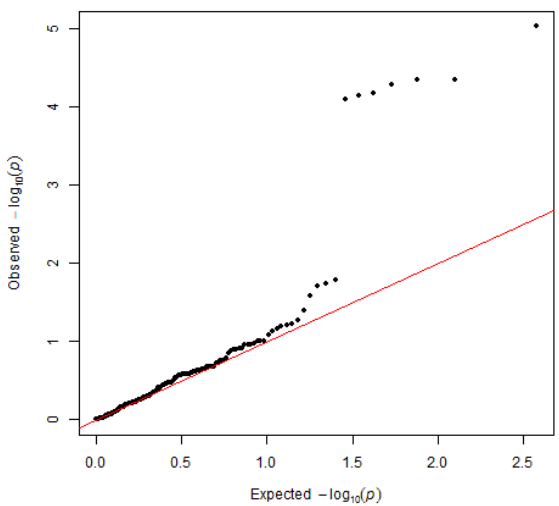


Figure 4.5. Average score of health behavior traits (corrected for age, sex, and familial correlation) by genotype and personality groups (significant results from GxP analysis)

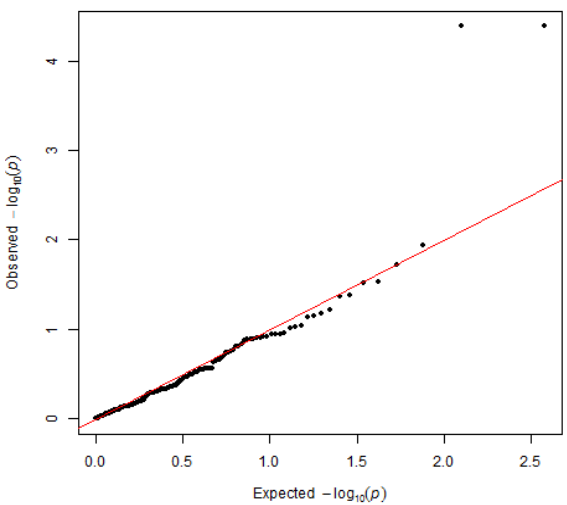
Figure 4.6. Q-Q plots for the significant results from Gene-by-Personality interaction analysis



DEBQ-EME & ST - rs363050 (SNAP25)
Lowest p value: 2.92E-05
Inflation Factor (λ): 1.24



DEBQ-EXE & SD - rs11160570 (EVL)
Lowest p value: 9.40E-06
Inflation Factor (λ): 0.97



FTND & CO - rs1006737 (CACNA1C)
Lowest p value: 4.12E-05
Inflation Factor (λ): 0.84

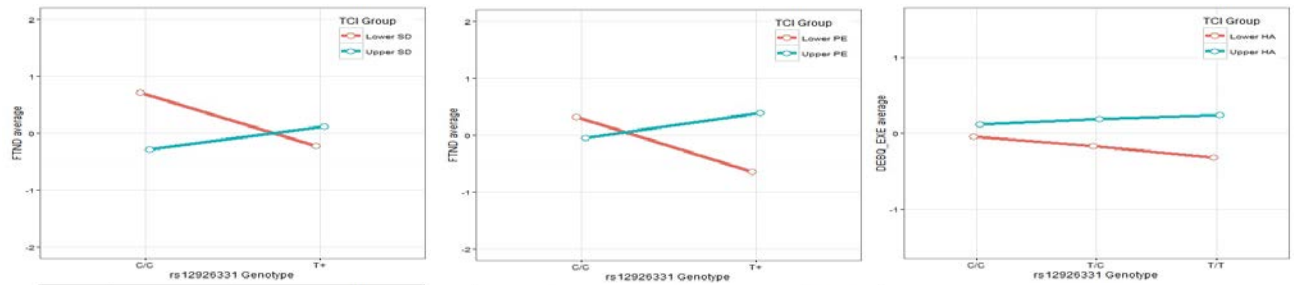
Table 4.17. Significant Gene-by-Personality interaction on health behavior traits among genetic variants associated with personality from Chapter 3

	TCI-Trait	CHR	SNP	Gene	G1-n	G1-BETA(S.E)	G2-n	G2-BETA(S.E)	P_GXE
FTND	SD	16	rs12926331	*CDH13*	333	-0.956(0.404)	634	0.401(0.291)	0.006
FTND	PE				279	-0.865(0.373)	689	0.422(0.311)	0.008
DEBQ-EXE	HA				1845	-0.129(0.050)	930	0.071(0.067)	0.017
DEBQ-EXE	RD	9	rs4745134	*RP11-274B18.4*	1807	-0.041(0.030)	898	0.088(0.039)	0.009
DEBQ-EME	NS				1829	-0.025(0.023)	905	0.079(0.046)	0.042
DEBQ-RSE	HA	15	rs56197244	*ADAMTS17*	1816	0.025(0.042)	926	-0.161(0.057)	0.009
DEBQ-EXE	NS				1822	-0.065(0.031)	904	0.055(0.042)	0.021
DEBQ-EME	CO				868	0.104(0.043)	1880	-0.009(0.028)	0.029

Adjusted for age, sex, and family correlation All rounded to the nearest hundredth

Abbreviations: TCI, Temperament and Character Inventory; S.E, Standard Error; DEBQ, The Dutch Eating Behavior Questionnaire; RSE, restrained eating; EME, emotional eating; EXE, external eating; FTND, Fagerstrom Test for Nicotine Dependence; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reword Dependency; PS, Persistence; SD, Self-Directedness; CO, Cooperativeness; ST, Self-Transcendence

Figure 4.7. Average score of health behavior traits by genotype (GWA findings from Chapter 3) and personality groups



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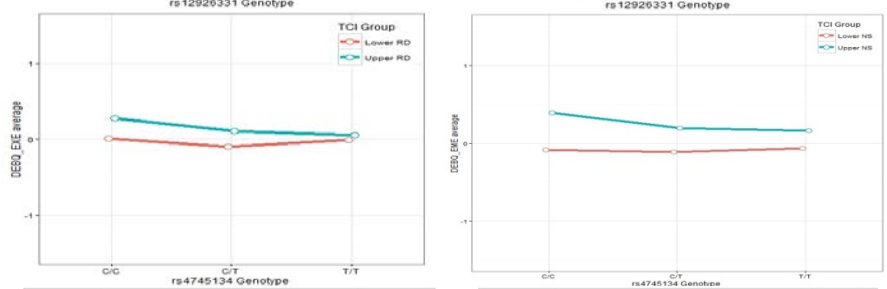

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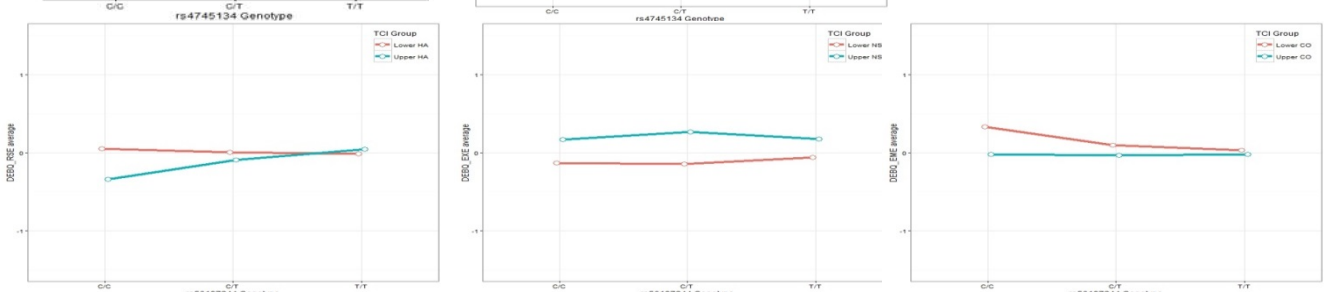

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4. Discussion

In this study, several traits of personality measured by TCI were observed to be related to wide range of risky health behavior traits that are the main preventable causes of mortality and morbidity worldwide. All problematic eating behavior traits, reported to be related to obesity and eating disorders [144-146], were positively associated with ST, which is a trait associated with spiritual aspects of oneself and self-consciousness [13]. On the other hand, individuals with high ST tend to have lower alcohol dependency. Having a persistent personality was observed in restrained eaters, which is constant with the restraint theory, where a person persistently restrains his or her diet for their desired physical stature [162]. Higher scores of NS and HA, and lower SD and CO was observed in emotional eaters and external eaters. Additionally, reward dependent individuals were more likely to be external eaters. Self-Directed ever smokers, who are characterized as responsible, purposefulness, and having strong ability to regulate oneself, had lower dependency for nicotine. Combination of high NS and RD score was observed in individuals with high alcohol dependency, and self-directed and cooperative individuals had lower scores of AUDIT.

Novelty seeking, a personality dimension characterized with impulsiveness and exploratory excitability by a novel stimulation, was positively associated with all of the targeted health behavior traits, which represents problematic engagement in health behaviors, except for restrained eating. Additionally, low SD and low CO are known as general factors predicting the presence of personality disorder [26, 163], which is also

observed in individuals with emotional eating behavior, external eating behavior, high nicotine and alcohol dependence in our study results. Individuals who were successful in smoking cessation had lower NS and higher SD than those who continued smoking, which is also constant with other findings. It was also found that NS was positively associated with BMI, waist circumference, total fat percent, and trunk fat percent in the previous study using the same subsamples of the Health Twin Study [164]. Negative associations between SD, CO, and obesity indices were also observed, which is consistent with the results for the External and Emotional eating behaviors. From the co-twin study, substantial environmental effect, which was higher compared to genetic effect, on the association between NS and obesity was found, which indicates that application of intervention for the treatment for both problematic eating behaviors and obesity targeting modifiable environment factors might be effective. Overall, the relationship between personality and health behaviors were identified, and problematic personality that can be associated with risky health behaviors were defined.

From the factor analysis of subscales of NS, SD, and CO, specific patterns of personality that are related to health behaviors were found. Individuals with high SD had low NS (factor1, Determinedness), and pattern of high NS along with low SD and CO was also observed (factor2, Vulnerability), which was recognized as vulnerable personality for risky health behaviors. The combination of this pattern was tested for association with eating behaviors and nicotine, alcohol dependency, and significant association was observed for all of the targeted health behaviors, thus

supporting our hypothesis that high NS and low SD and CO may predict harmful health behaviors. Directions of causalities from Vulnerability to all risky health behavior traits were also observed. All of the coefficients for the direct causal effect of Vulnerability on these health behaviors were positive, which indicates that more a person has vulnerable personality, more likely to engage in risky health behaviors. For dependency traits, education and income level showed substantial negative effect on the health behaviors, indicating its important role in the complex etiology of health behavior development. Also from the prediction model assessment, the results indicated that adding Vulnerability to prediction of eating behaviors or alcohol dependencies to a simple age model can improve the prediction of disease. The findings from this study shows that risky health behavior prediction models comprising personality traits can be applied to adolescents who has not yet fully established their personality, and also has not developed risky health behaviors yet for prevention purposes targeted for both personality and health behavior interventions.

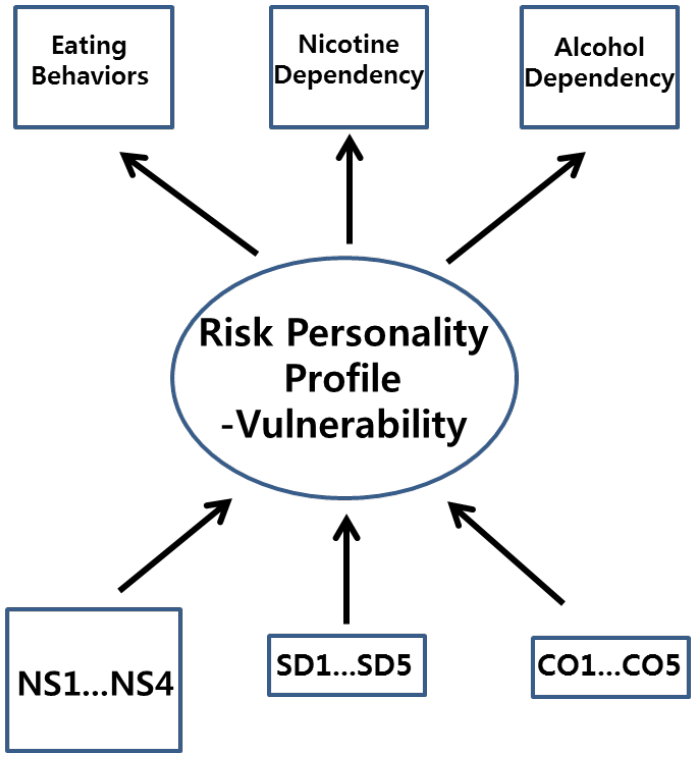

Figure 4.8. Components of defined risky personality profile and its effect on targeted health behaviors

Genetic markers may also play a role in health behavioral traits, and many GWA studies are being conducted discovering novel genetic variants that are either directly or indirectly associated with wide varieties of health behaviors [165-167]. Evidenced by the association between health behaviors and personality traits, a hypothesis that personality will modify the effect of gene on these heath behaviors was set. The targeted health behaviors have psycho-social aspects in their theoretical models, and are known to be associated with neurotransmitters such as dopamine [168, 169] and/or serotonin [170]. Noting that temperament dimensions of TCI were factorized

based on these neurotransmitters theoretically, and personality may represent certain biological process in human body [57], 183 genetic variants that were reported to be associated with neurotransmitters, behaviors, and other neuro-psychological traits or disorders were selected to search for GxP effect. The list also includes three genetic loci that were suggested to be associated with personality in chapter 3. This list contains genetic variants reported to be related to psychological traits from many different fields of study, including molecular genetics and epidemiology, which might give us insight into physiological mechanism on how genes or genes interacting with personality influence certain onset of health behaviors.

From our study, there were three genetic loci that interacted with personality to modify the health behaviors. Individuals with lower ST scores showed additively increased emotional eating behavior with G allele of rs363050 (*SNAP25*), but higher ST group had decreased degree of emotional eating by the genotype. *SNAP25* gene was reported to be involved in the regulation of neurotransmitters, and showed relationship with Attention Deficit Hyperactivity Disorder (ADHD) [171] and intelligence [172]. Several SNPs in *EVL* had interacting effect with SD on external eating behavior. Lower SD group showed decreasing average score of external eating behavior by T allele of rs11160570, whereas individuals with higher SD scores displayed increasing trend of external eating. *EVL* is known to be related to immune system pathway and is involved in actin binding. It was reported from a GWA study that *EVL* is associated with paranoia, which is a component of hostility [173]. Lastly, lower CO group had higher nicotine

dependency among individuals with A+ allele of rs1006737 of *CACNA1C*, but opposite direction of trend was observed for individuals with high CO. *CACNA1C* is a gene that encodes an alpha-1 subunit of a voltage-dependent calcium channel, and it is reported to be related to bipolar disorder from a GWA study [174].

With the results of this study, genetic characteristics and personality elements were confirmed to act in concert to affect one's engagement in risky health behaviors. Many studies reported GxP interactions [74, 76, 77, 79, 175], but to our knowledge, this is the first study that explored interacting effect of various genetic variants and personality on wide range of health behaviors. The modifying effect of personality on the genetic predisposition in developing certain health behaviors are observed, but it is also important to translate the results into practical intervention strategies. To note, genes are not subjectable for modification, and personality also is a relatively stable trait; from chapter 2 of this study, only NS showed decreasing trend with aging, and SD showed slight evidence of converge after long-term close relationship such as being a spouse. Personality may be mutable when interventions [176-178] or pharmacological treatments [179] are applied, especially for adolescents or children, but the target for intervention integrating personality and gene should be recognizing the difference, rather than modification of their own.

With the results of this study, the aim is to identify at-risk individuals. For instance, individuals with A allele of *SNAP25* SNP and high ST are more

likely to have emotional eating behavior than individuals with low ST. Also, individuals with A allele of *CACNA1C* SNP and low CO may have more risk of developing nicotine dependence than ones with A allele and high CO. Same applies to SD and *EVL* SNP's effect on external eating behavior. It was reported that a standard intervention was less effective for individuals with particular personality (i.e. sensation seeking and impulsive decision-making) [180]. Also for the addictive behaviors, one could engage in substance abuse because of high anxiety and use the substances for means to cope with emotion. Contrarily, impulsive individuals may be addicted to drug due to lack of control [181]. Even if individuals exhibit certain type of health behavior patterns, underlining effect of combination of gene and personality may vary. Form this point of view, comprehensive treatment model incorporating different focus and reinforcements by specific genotypes and personality is required for effective treatment of risky behavioral patterns.

We are currently in the era of personalized medicine, which is especially relevant in shaping one's behaviors related to health. From this study, it was found that personality is strongly associated with various types of risky health behavior traits, which are important contributors for overall mortality and morbidity by cancer, cardiovascular disease and other complex and common diseases. Joint effect and interaction between gene and personality was also observed, indicating their role in the likelihood of health behavior change. The cost of genotyping is decreasing and the tools measuring personality are inexpensive. By using combination of both factors, potent and cost-effective prevention and intervention can be applied for

modification of risky health behaviors, but some cautions are required because of the complexity of targeted traits. Nonetheless, current standard interventions, which are used universally despite the evident individual differences, need updates in order to effectively treat conditions.

V. Summaries and Conclusion

As the emphasis on the personalized medicine increases, the demand for translating the genetic epidemiological findings to clinical usage has been recognized, especially with the advances in genomic technologies and mass accumulation of genetic database worldwide. The Institute of Medicine's report titled "The Future of the Public's Health in the 21st Century" [182], highlights individual's genetic characteristic's complex interacting play with wide range of factors in shaping one's health, and its role in prevention of certain disease even before the onset and identification of biological background of health conditions. Therefore, understanding of interaction among genes, and interaction between gene and many other environmental factors including personality are important, and more studies dissecting the multiple levels of health factors are very essential for future of precision medicine and public health incorporating various factors. From this point of view, genetic and environmental structures of personality traits, which also can be integrated into precision medicine, were dissected in this study (Figure 5.1).

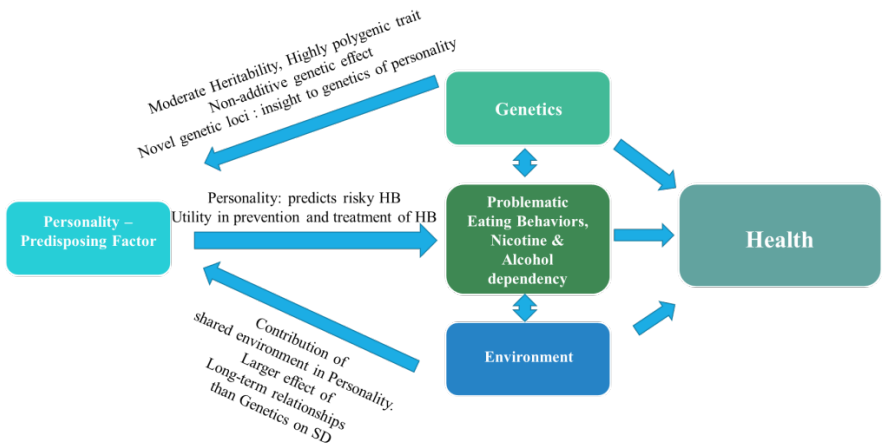

Figure 5.1. Framework of this study, revisited (adapted from PRECEDE-PROCEED model [61, 62])

With wide variety of family relationship types, moderate heritability of 15~44% on all dimensions of personality was estimated, as well as significant contribution of non-additive genetics to personality traits measured by Temperament and Character Inventory. Substantial effects of long-term shared environment between close relationships on personality, especially on character traits, were also observed. Moreover, the roles of temperament and character domains in personality development were distinguishable. Because personality traits are complex and polygenic genetic effects are expected for them, finding a single locus that influences individual's personality has been elusive even in highly powered studies with Caucasian samples. In the current study of genetic epidemiology of personality, three candidate regions that may have associations with personality traits in a Korean population were identified by using variety of personality measures and incorporating multiple dimensions together. The study results need replications, but the findings can provide additional information to the body of knowledge on personality genetics. In order to surely dissect the biological background of personality development, further study with large sample size, variety of ethnicity, and study design incorporating multiple measures of personality should be considered. Effects of non-additive genetic, such as interactions within multiple genes, and rare variants should also be inspected.

The contributions of personality on wide range of health behaviors were also confirmed. Specifically, high NS, low SD and low CO were constantly observed in individuals with risky health behaviors, and their combined effect, named Vulnerability, on eating behaviors and nicotine /

alcohol dependence was observed. Causal effect of Vulnerability on the health behaviors were confirmed, and it was also shown that personality traits have the ability to predict eating behaviors and alcohol dependencies, indicating its' importance in prevention and treatment of the problematic health behaviors. Additionally, genetic variants that modify the effect of personality traits on targeted health behaviors were found.

Findings of this study highlight the importance in integrating personality profiles to individualized intervention strategies. Recognizing that universal standard approach will have diverse treatment outcomes in individuals with different genetic and personality characteristics is important. Also, it is also important to consider other environmental factors that might interact with personality in the process of development of certain health behaviors, since the total variation of these health behaviors are not wholly explained by personality only. From the PRECEDE-PROCEEDE model, it has been emphasized that other predisposing factors (i.e. knowledges, values, skills), reinforcing factors (i.e. social norms, political advocacies, social networks), and enabling factors (i.e. health insurance, community resources) can also affect individual's behaviors, and complex interplay between these factors and personality is expected in development of certain health behaviors. Additionally, in an event of life crisis that has influence on almost every aspects of individual's life, personality may interact with the crisis, since individuals with different personality will react differently to events. From this perspective, the complexity of health behavior development in the viewpoint of personality should also be reflected in developing treatment

models. In ecological models incorporating many factors from individual, interpersonal, organizational, community, and public policy level that determine one's engagement in risky health behaviors, this study took place in assessment of personality's genetic and environmental background, which is leveled at the bottommost of the ecological model, and its effects on development of certain health behaviors that are related to preventable causes of mortality and morbidity worldwide were examined. However personality explains only a part of variations in these health behaviors, and many other factors in the ecological models will interact with personality or have direct effect on individual's health. Therefore, when interpreting the results of the current study, placing emphasis on the consideration of the holistic model is important.

As studies on genomics of human health is being constantly conducted and effect of gene being discovered, shifting of practice in medicine has started. Currently, genetics are used not only for prevention or diagnostics, but also for treatment of certain diseases. However, concerning voices in personal rights and health equity is being raised constantly [182]. Besides issues such as privacy, insurance, stigmatization by genetic characteristics and etc., and despite the fact that cost of genotyping is decreasing, incorporating genetics in mainstream of health care may provoke widening of the social gap and public health inequity, consequently impacting the quality of life for those who does not have opportunity to benefit from precision health. Personality measurement may also have the same concern when incorporated in prediction and prevention policies of health conditions.

Therefore, when policies regarding the usage of personal factors (i.e. genetic predisposition, personality characteristics) in prediction and treatment of health are being developed, cautious application is very crucial especially in the point of view of social ethics.

The next step for the researchers will be translating and integrating the epidemiological findings into personalized medicine. By doing so, healthcare providers can identify at-risk individuals who are vulnerable to risky health behaviors, consequently resulting in preventions of diseases and health improvements.

VI. References

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VII. Supplementary Martials: sTable 1. Summary of reported genome-wide association studies on personality trait

Personality Trait	Author (publish year)	Samples			Method		Result			
		Consortium	# of Samples	Survey Version	Platforms / Imputation Ref.	Association	Top SNP	P-value	Replication	Gene-Base / etc. results
Cloninger's Temperament	Verweij et al. (2010)	Two cohorts of Australian twins and their families (European ancestry) -QIMR	5117 (1727 males and 3390 females) from 2567 independent families	Tridimensional Personality Questionnaire - Short	Illumina 317K, Illumina HumanCNV370-Quadv3, Illumina Human610-Quad, and Affymetrix 6.0 /European HapMap 1 + 2, Release 22 Build 36	family-based association test as implemented in Merlin (-fastassoc)	HA-rs11780799 (NCALD)	1.10E-05	NA	HA-SLC7A14 (7.8×10-5)
							NS-rs4131099 (Intergenic)	3.80E-06		NS-FLG2 (4.0×10-6)
							RD-rs1078425 (CEP120)	9.80E-06		RD-SLIT2 (2.8×10-5)
							PE- rs12753569 (Non-coding region)	7.60E-06		PE-KIAA0427 (2.0×10-6)
	Service et al. (2012)	The Northern Finland Birth Cohort (NFBC)	4508	TPQ subset of the TCI version 9 - 107 binary items	NFBC-Illumina 370duo Chip, YFS-Illumina 670K Custom BeadChip, HBCS-Illumina 610K Quad Chip, QIMR-listed above / HapMap2 (HM2)	probABEL (Additive model) / QIMR-Merlin	HA-rs17680945 (APBA2)	1.59E-06	Replication with de Moor et al. not found (openness to experience (rs1477268 , rs2032794) conscientiousness (rs2576037))	HA-WDR63 (0.00001)
		The cardiovascular risk in young Finns (YFS)	1383	TCI version 9 with 240 Likert items			NS-rs1494508 (MSRB3)	1.87E-06		NS-MSRB3 (0.00005)
		The Helsinki Birth Cohort Study (HBCS)	1425	TPQ version 4 with 98 binary items			RD-rs2833693 (C21orf45)	2.82E-07		RD-AMPD2 (0.00004)
		The Australian twin registry (QIMR)	5117	Tridimensional Personality Questionnaire - Short			PE-rs17608059 (COX10)	3.60E-06		PE-XYLB (0.00009)
NEO Personality Inventory (NEO-PI-R) /Big 5	Terracciano et al. (2010)	Sardinia, Italy	3972 individuals (2250 women and 1722 men)	Italian version of the NEO-PI-R, a 240-item	Affymetrix 10K and Affymetrix 500K/Lander–Green algorithm(based on the genotypes of family members)	Merlin (in the context of a variance component model that accounts for resemblance among related individuals)	N-rs6047641 (-)	6.54E-06	0.16	
		Replication - Tecumseh, MI, USA	923 individuals (110 unrelated individuals and 813 individuals clustering in 424 families)	NEO-PI	25 SNPs were genotyped using TaqMan SNP genotyping assays		E-rs644148 (ZNF180)	8.03E-06	0.335	
		Replication - Netherlands Twin Register	1158 individuals from 418 families	Dutch version of the NEO-FFI	Sequenom technology		O-rs644148 (ZNF180)	9.44E-07	NA	
		Replication - Erasmus Rucphen Family study	1822 participants	NEO-FFI	TaqMan		A-rs1380251(-)	1.64E-06	0.375	
							C-rs11626232 (SMOC1)	4.82E-06	0.112	

Personality Trait	Author (publish year)	Samples			Method		Result			
		Consortium	# of Samples	Survey Version	Platforms / Imputation Ref.	Association	Top SNP	P-value	Replication	Gene-Base / etc. results
NEO Personality Inventory (NEO-PI-R) /Big 5	de Moor et al. (2012)	Discovery-SardiNIA—Italy, NTR/NESDA—the Netherlands, The Erasmus Rucphen Family (ERF) study, The Study of Addiction: Genetics and Environment (SAGE), The Helsinki Birth Cohort Study (HBCS), Nicotine Addiction Genetics study (NAG)-Australia, QIMR study—Australia, The Lothian Birth Cohort (LBC) study-UK,Baltimore Longitudinal Study of Aging, Estonian Genome Project of University of Tartu (EGPUT)	17 375 adults	240-item NEO-PI-R, NEO-FFI	studies used Illumina platforms, except for SardiNIA and NTR/NESDA, which used Affymetrix and Perlegen platforms, respectively /HapMap phase II CEU data	linear regression (under an additive model)/SNPTEST, taking the uncertainty of the imputed genotypes into account/MACH QTL/ Related - Merlin (varaince components approach)	O-rs1477268, rs2032794 (RASA1)	Discovery-2.8 E-8, 3.1E-8 Pooled all-1.84E-6, 1.70E-6	0.53, 0.55	N-PTPLA (2.60E-05) E-AHCYL1 (5.60E-05) O-MOGAT1 (1.00E-06) A-WSB1 (2.80E-05) C-TCEB3B (1.00E-07)
		Replication- NTR+—the Netherlands, German cohort, EGPUT2—Estonia, Cilento—Italy, ERF2—The Netherlands	3294 subjects	NEO-FFI			C-rs2576037 (KATNAL2)	Dscovery-4.9 E-8 Pooled all-1.02 E-7	0.36	
	van den Berg (2015)	Twenty-one cohorts were from Europe, six from the United States and two from Australia.	63,030 subjects in 29 cohorts	Extraversion scales of the NEO Five Factor Eysenck Personality Questionnaire/ Reward Dependence scale of the Cloninger's TCI / Positive Emotionality scale of the Multidimensional Personality Questionnaire	Illumina or Affymetrix platforms /imputed using the 1000Genomes phase 1 version 3 (build37, hg19) reference panel	Extraversion scores were regressed on each SNP under an additive model, with sex and age included as covariates.	rs2024488 - LOC101928250	2.9 x 10-7	0.08244	LOC101928162 (P = 2.87 x 10-6)
		The Generation Scotland: Scottish Family Health Study (GS:SFHS) cohort was included as a replication sample .	9,783 subjects				74 SNPs with P-values<1 x 10-5.			
	de Moor et al. (2015)	29 discovery cohorts, with 21 cohorts from Europe, 6 from the Unites States and 2 from Australia.	63,661	Neuroticism from the NEO Personality Inventory / harm avoidance from the Cloninger's TCI - harmonized across all cohorts by Item Response Theory (IRT) analysis	Illumina or Affymetrix platforms /1000G phase 1 version 3 (build 37, hg19) reference panel	linear regression (additive model, with sex and age as covariates). account. In those cohorts that included related individuals, the dependency among participants was accounted for.	rs35855737-MAGI1/ Eleven other SNPs in the MAGI1 gene showed suggestive genome-wide significance	9.26E-09	not replicated, 0.32 but the direction of the effect is the same	
		The Generation Scotland cohort	N=9,786							

Personality Trait	Author (publish year)	Samples			Method		Result			
		Consortium	# of Samples	Survey Version	Platforms / Imputation Ref.	Association	Top SNP	P-value	Replication	Gene-Base / etc. results
Non-European NEO Personality Inventory (NEO-PI-R) /Big 5	Kim et al. (2013)	Young Women Cohort in Korea	1089 young women	NEO-PI-R-90-item	Illumina Human 1 M-Duo DNA Analysis BeadChip/ 90 individuals of JPT, CHB of HapMap release 23	linear regression - PLINK	N-rs10106540 (ST3GAL1), rs12601685(OR1A2)	4.59E-7, 3.20E-5	0.15, 0.05	SNP rs2576037 in KATNAL2 (C) not associated with this trait in our study (P=0.395)
		Replication-Kangbuk Samsung Cohort Study	2090 young women		Fluidigm SNPtype Assay - selected 40 SNPs among the top 30 ranked SNPs of each factor		O-rs2146180 (PTPRD)	1.67E-08	0.14	
	Kim et al. (2015)	Korean Association Resource phase 3, The Young Women cohort in Korea	Ansung -1126, Ansan 1683, 1089 women aged 18~40 Total-3898	NEO PI-R 90-item questionnaire	Affymetric Genome-Wide Human array 5.0, Illumina Human 1M-Duo DNA Analysis BeadChip/ HapMap3 release 2 (JPT+CHB, 1.39M), and Korean HapMap panel data (1.66M)	linear regression under an additive genetic model by PLINK	N-rs1010657 (TACC2)	8.79E- 7	NA	The association between conscientiousness and KATNAL2 was observed in this study (P=0.038, Supplementary Table 4).
							E-rs12537271 (PTPN12)	1.47E-07	0.898	
		Replication- The Healthy Twin study	1021 participants		Affymetrix Genome-Wide Human array 6.0 (Affymetrix, Inc.) or Illumina Infinium HumanCore-12 Beadchip (Illumina)/1000 Genome Asians	The Family-based Score Test for Association in the GenABEL	O-rs16921695 (IMPAD1)	2.26E-06	0.272	
							A-rs8015351 (RPS29)	1.27E-06	0.969	
							C-rs912765 (LMO4)	2.91E-06	0.448	

sTable 2. List of neurodegenerative disease, neuro-psychological disorders or traits related genetic variants collected from Eu-pedia (http://www.eupedia.com/genetics/medical_dna_test.shtml) and SNPedia

Gene	SNP	Function, Reported relationship to psychosocial, behavioral phenotypes
ADRA1A	rs1048101	1a adrenoceptor
ADRA2A	rs553668	2a adrenoceptor
	rs1800544	
	rs11195419	
	rs521674	
ADRBK2	rs3730315	ADHD
AM	rs669	Alzheimer's Disease
ANKK1	rs1800497	Obsessive-Compulsive Disorder Addictive behaviours (gambling, alcoholism, smoking...) Alcoholism (other) Intelligence (learning from errors) Dopamine D2 Receptor gene
APC	rs1804197	Autism (Asperger's syndrome)
	rs2229992	
	rs42427	
	rs465899	
APPL2	rs2272495	Autism
AVPR1A	rs10784339	Emotional commitment
	rs11174811	
BCR	rs140504	Bipolar disorder
	rs2156921	Depression
	rs2267012	
	rs2267015	
	rs3761418	
BDNF	rs11030104	Alzheimer's Disease
	rs6265	ADHD, Depression Intelligence / IQ (cognitive abilities, attention, memory) Alzheimer's Disease
CACNA1C	rs1006737	Bipolar disorder
	rs2159100	
CAMTA1	rs4908449	Memory (episodic)
CHRM2	rs1378646	Intelligence / IQ
	rs2350780	
	rs324640	
	rs7782965	

	rs7810473	
	rs1824024	Depression
	rs2061174	Depression, Intelligence / IQ
	rs324650	
CHRNA3	rs1051730	Nicotine dependence
	rs3743078	
	rs578776	
CHRNA5	rs16969968	Cocaine dependence, Nicotine dependence
	rs637137	Nicotine dependence
CHRNA6	rs2304297	Nicotine dependence
CHRNB3	rs10958726	Nicotine dependence
	rs6474413	
CHRND	rs2767	Nicotine dependence
	rs6749955	
CLOCK	rs1801260	ADHD, Sleeping time (later)
CLSTN2	rs6439886	Memory (episodic)
CNTNAP2	rs2710102	Autism (delayed onset of speech)
COMT	rs165599	Schizophrenia, Hyperactivity
	rs2097903	Hyperactivity
	rs4633	
	rs6269	
	rs737865	Schizophrenia
CROT	rs802026	Progressive Supranuclear Palsy
	rs802028	
	rs802030	
DAPK1	rs4877365	Alzheimer's Disease
	rs4878104	
DCDC2	rs793862	Dyslexia
	rs807701	
DGKH	rs1012053	Bipolar disorder
DISC1	rs1322784	Autism (Asperger's syndrome)
	rs3738401	Schizophrenia
	rs821616	Intelligence (less cognitive decline with age)
DPP6	rs10239794	Amyotrophic Lateral Sclerosis (ALS)
DRD2	rs1076560	Alcoholism (other)
	rs4648317	Nicotine dependence

	rs6276	aldehyde dehydrogenase 2
	rs6277	Schizophrenia
DRD3	rs6280	Obsessive-Compulsive Disorder
DRD4	rs180095	Novelty-seeking behaviour
DTNBP1	rs1018381	Schizophrenia
	rs2619522	Schizophrenia, Intelligence / IQ (cognitive abilities, attention, memory)
	rs760761	
	rs2619528	Intelligence / IQ (cognitive abilities, attention, memory)
	rs2619539	
	rs3213207	
EIF2AK2	rs2254958	Alzheimer's Disease
EVL	rs11160570	Progressive Supranuclear Palsy
	rs2181102	
	rs3783332	
	rs3783337	
	rs7158754	
	rs7159195	
	rs941898	
FADS2	rs1535	Intelligence (higher IQ if breastfed)
	rs174575	
FAM47E	rs6812193	Parkinson's Disease
FKBP5	rs7757037	Bipolar disorder
FLJ10986	rs10493256	Amyotrophic Lateral Sclerosis (ALS)
	rs1470407	
	rs6587852	
	rs6690993	
	rs6700125	
GAB2	rs2373115	Alzheimer's Disease
GABBR2	rs2779562	Nicotine dependence
	rs3750344	
GABRA2	rs279836	Alcoholism (alcohol dependence)
	rs279845	
	rs279858	
	rs279871	
GHSR	rs2948694	Alcoholism (other)
GNB1L	rs2269726	Schizophrenia

GOLM1	rs10868366	Alzheimer's Disease
HES1	rs4686673	ADHD
HTR1A	rs6294	9-HT receptor that binds the endogenous neurotransmitter serotonin ersons with the G-allele of the polymorphism may have higher personality score for the NEO PI-R Neuroticism and TPQ Harm Avoidance traits
	rs6295	
HTR2A	rs6311	Progressive Supranuclear Palsy
	rs6313	
HTR3C	rs6807362	Autism
IL18RAP	rs3771150	Amyotrophic Lateral Sclerosis (ALS)
intergenic	rs2352908	Autism (social communication problem)
	rs10519262	Alzheimer's Disease
	rs12473579	Amyotrophic Lateral Sclerosis (ALS)
	rs1460163	Creutzfeldt-Jakob Disease
	rs17027230	Amyotrophic Lateral Sclerosis (ALS)
	rs17101921	Schizophrenia
	rs2235749	Cocaine dependence
	rs35753505	Memory
	rs910079	Cocaine dependence
	rs910080	Cocaine dependence
	rs9886784	Alzheimer's Disease
ITGA4	rs1143674	Autism
KIAA0319	rs761100	Dyslexia
KIBRA	rs17070145	Memory (episodic)
LOC653748	rs10260404	Amyotrophic Lateral Sclerosis (ALS)
LOXHD1	rs988213	Amyotrophic Lateral Sclerosis (ALS)
MAGI2	rs757863	Amyotrophic Lateral Sclerosis (ALS)
MAPKAP1	rs536861	Autism
MCCC1	rs10513789	Parkinson's Disease
ME2	rs642698	Epilepsy
MME	rs1836915	Alzheimer's Disease
MPO	rs2333227	Alzheimer's Disease
NR1H3	rs7120118	Progressive Supranuclear Palsy
OLR1	rs1050283	Alzheimer's Disease
OPRD1	rs12749204	Cocaine dependence
OPRM1	rs1799971	Alcoholism (alcohol cravings), Heroin addiction
OXTR	rs2254298	Pair-bonding (+ sociability)associated with increased oxytocin receptors in the brain.
	rs75775	

PALB2	rs420259	Bipolar disorder
PDE11A	rs3770018	Depression
PLAU	rs2227562	Alzheimer's Disease
PRNP	rs1799990	Memory (long-term; logical) Creutzfeldt-Jakob Disease Primary progressive aphasia
PVRIG	rs1445442	Autism
RGS2	rs4606	Social Phobia
SERT(5HTT)	rs1042173	Alcoholism (other)
SHANK3	rs9616915	Autism
SIRT1	rs3758391	Intelligence (less cognitive decline with age)
SLC18A1	rs2270641	Schizophrenia
SLC1A1	rs3780412	Glutamate transporter gene
SLC1A3	rs2269272	ADHD
SLC6A4(SERTor5HTT)	rs140701	Social Phobia
	rs3794808	
	rs4583306	
SLC9A9	rs1242075	ADHD
SNAP25	rs363050	Intelligence / IQ (non-verbal)
	rs363026	ADHD
	rs3746544	
	rs6039806	
SNCA	rs356219	Parkinson's Disease
SORL1	rs2070045	Alzheimer's Disease
	rs641120	
	rs668387	
	rs689021	
TMEM165	rs534654	Bipolar disorder
TNF	rs1799724	Alzheimer's Disease
TPH1	rs1799913	Depression, Heroin addiction
	rs1800532	Schizophrenia
	rs211105	
	rs7933505	Depression, Schizophrenia
TPH2	rs11178997	Bipolar disorder
	rs1386493	ADHD
	rs17110747	
	rs1843809	
	rs4290270	Heroin addiction

	rs4565946	Anxiety, Obsessive-Compulsive Disorder
	rs4570625	Anxiety Bipolar disorder Obsessive-Compulsive Disorder
	rs7305115	tryptophan hydroxylase 2, linked to several psychiatric and/or behavioural phenomena, early-onset obsessive compulsive disorder susceptibility to suicide.
	rs7963720	Heroin addiction
TTRAP	rs2143340	Dyslexia
USP24	rs287235	Parkinson's Disease
USP40	rs838552	Parkinson's Disease

VII. 국문 초록

성격의 결정요인과 성격 유형이 위험 건강행동에 미치는 영향

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성격은 거의 모든 개인의 심리적, 육체적 상태에 중요한 역할을 한다. 또한 개인의 성격은 특정적인 건강 행동을 발생시키는 가능성을 높여 건강에 영향을 미치기도 한다. 이러한 관점에서 성격 유형을 임상에 개입시키는 것을 강조하는 많은 건강 행동 이론들이 발표 되었다.

Temperament and Character Inventory(TCI)는 행동 유전학에 널리 사용되는 포괄적인 성격 인벤토리이다. 본래의 모델 이론에서는 기질(Temperament) 특성은 유전적 영향 하에 있다고 제안하였고, 반면 성격(Character)특성은 성인기의 초기 시기까지 기질과 환경 사이의 상호 작용에 의하여 영향을 받는다. 성격의 유전율은 평균적으로 0.4정도로 보고되어 있지만 인종간에 불일치가 존재하고, 이 추정치는 쌍둥이들만 사용된 연구에서는 부풀려져서 추정되는 경향이 있다. 또한, 대부분의 성격 도메인에 대한 유전율이 작지 않은 0.3~0.6 임에도 불구하고, 연구 파워가 큰, 백인 샘플을 사용한 연구에서 조차도 성격을 설명하는 특정 유전자 변이를 찾는

데 실패하였다. 성격의 결정요인을 확인하는 것뿐만 아니라 성격과 위험한 건강 행동, 특히 심리적 기반을 가지고 이론화시킨 모델로 측정된 건강행동과의 관계를 확인하는 것은 중요한 공중 보건학적 의미를 제공할 수 있다. 또한 성격이 건강행위에 대한 유전자의 효과를 중재할 수도 있다.

본 연구에서는 성격에 유전적 요인과 환경적 요인의 기여도를 측정하여 배우자 효과에 특별한 주의를 두면서 TCI의 모델을 평가하였다. 또한, 서양 인구와는 문화 환경이 다른 한국의 인구집단을 대상으로 TCI와 Five Factor Model (FFM)의 각각 유형의 전장 유전체연관 분석뿐만 아니라 다변수 TCI-FFM 모델 또한 분석이 수행되었다. 마지막으로 개인의 성격 특성과 섭식행동, 니코틴 의존증, 알코올 의존증 등의 건강 행태간의 연관성을 확인하였고, 심리적 특성과 관련된 것으로 보고 된 유전자 변형과 성격의 건강 행동에 대한 상호작용 효과를 탐구하였다.

이 연구는 한국의 the Health Twin Study에서 총 3,479명 (1,419명의 남성, 690 가족, 552 일란성 쌍둥이, 119 이란성 쌍둥이)을 포함하고 있으며 상세한 역학, 임상정보와 성격유형들의 정보가 측정되었다. 성격에 기여하는 유전 및 공유되는 환경을 확인하기 위해 Intraclass correlation coefficients (ICCs)와 유전율이 계산되었다. 이 참가자 중 3,428명이 TCI의 단변량 전장유전체 연관성 분석에 포함되었다. 이 중 1,169명 (476명의 남성) 이 FFM 설문을 수행하였다. 유전자형을 측정하기 위해 두 개의 플랫폼이 사용되

었고 (Affymetrix Genome-Wide Human array 6.0, Illumina Infinium Humancore Beadchips), 1kG의 아시아인들을 사용하여 imputation이 수행되었다. 단변량 분석은 가족 기반 연관성 테스트를mixed-effect variance component approach를 사용해 수행하였고, TCI-FFM 모델의 다변량 분석은 multiple family-based quasi-likelihood score test (MFQLS) 가 선형 혼합 모델의 여러 표현형과 유전자 변형의 관계를 추정하기 위해 사용되었다. 연령, 성별, 교육, 소득 수준, 그리고 가족간의 상관성을 보정하여 TCI 성격 요인들과 건강행위에 대한 선형 관계가 분석되었다. 건강 행동 요인들로는 Dutch Eating Behavior Questionnaire (DEBQ, n=3,444), Fagerstorm Test for Nicotine Dependence (FTND, n=1,192), 그리고 Alcohol Use Disorders Identification Test (AUDIT, n=2,431) 등이 사용 되었다. 대상이 된 건강 행동과 공통적으로 연관된 것으로 관찰 된 Novelty Seeking (NS), self-directedness (SD), Cooperativeness (CO)에 관해서 요인 분석이 principal component analysis를 사용해 수행되었고, 확인된 성격 패턴과 건강 행위와의 연관성을 분석을 하였다. 신경-심리학적 특성과 관련되어 있는 것으로 보고 된 183개의 유전자 변이가 건강 행태에 gene-by-personality (GxP) 효과 가 있는지 확인하였다.

유전적 기여도는 모든 TCI 유형에 대해 발견이 되었고 (0.15~0.44), harm avoidance (HA)와 모든 character 유형들에서 공유 환경의 효과가 (0.12~0.29) 확인 되었다. 일란성 쌍둥이간의

ICC는 0.36~0.46이었고, 부부들은 기질에 관해서는 적은 유사성을 보였지만 character 유형에서는 first degree 가족들(0.10~0.27) 보다 높은 유사성을 보였다 (0.27~0.38). 배우자 사이의 유사성은 대부분의 character 유형과 HA에서 결혼 기간에 따라 증가하는 추세를 보였다. 이러한 배우자 간의 유사성이 그들의 일란성 쌍둥이와 비교되었을 때 (84개의 트리오에서), character 유형 중 하나인 SD에서 결혼기간이 증가할수록 쌍둥이 형제보다 배우자간의 유사성이 커지는 것이 확인 되었다 (r=0.29). 전장유전체분석에서는 TCI중에서 CO 도메인이 ADAMTS17 유전자와 (Chromosome 15, p= 9.0e−8) 상관성을 보였지만 다른 도메인들은 전장유전체유의 수준에 도달하지 않았다. FFM의 agreeableness 결과에서는 CDH13 유전자 (Chromosome 16, p=2.8e−7)가 마지널한 p값을 보였고, 이전에 보고된 연구에서 이 유전형은 또한 agreeableness와 관련성을 보였다 (p=0.046). 다변량 분석에서 SD (TCI) 와 neuroticism (FFM)는 RP11−274B18.4 유전자 (r=−0.56, Chromosome 9, p= 7.52e−9)와 연관성을 보였다. 모든 일곱 TCI 유형들은 이 연구에서 목표된 건강 행동들과 어느 정도 관련성을 보였다. 그 중 높은 NS, 낮은 SD, 낮은 CO의 조합은 감정적인 식사행동, 외부적 요인으로 인한 식사행동, 니코틴 의존도 및 알코올 의존도에서 연관성이 관찰되었다. 이러한 도메인들의 하위척도들은 특정한 성격 프로파일을 확인하기 위해 요인분석이 되었고, 관찰된 성격 프로파일인 Vulnerability가 위험한 건강 행동과의 연관성이 있고 이를 사용하

여 위험한 건강행동의 예측이 가능한 것이 확인되었다. SNAP25 유전자는 감정적인 식사행동에 관한 연관성에 self-transcendence와의 상호작용을 보였고, EVL유전자의 외부적 요인으로 인한 식사행동에 대한 효과에서 SD와 상호작용을 보였다. 또한 CACNA1C 유전자는 CO와 상호작용을 하여 FTND에 영향을 미쳤다.

연구 결과를 통해서 확인된 후반 성인기에서의 SD 변화는 TCI의 성격 도메인이 동일하게 유전적 영향을 받음에도 불고하고 뚜렷이 다른 발달 방식을 가지고 있다는 정신-생물학적 이론을 지원한다. 또한, 새로운 성격관련 유전자좌, 특히 character dimensions에 관련된 유전 변이를 밝힐 수 있었고 이러한 전장 유전체 검색에서의 결과는 한국인의 성격 특성에 다른 생물학적 배경이 있을 수 있음을, 또한 다수의 성격 유형이 그러한 성격의 배경을 더 잘 캡쳐 할 수 있음을 보여준다. 마지막으로, 특정 위험 건강 행동을 야기 시키는 성격 패턴과 GxP효과를 발견함으로써 이러한 결과를 위험한 건강 행위와 그에 따른 질병에 대한 효과적인 예방과 중재를 위한 맞춤 위학으로 translate할 수 있을 것이다.

주요어: 성격, 유전 역학, 유전율, 전장유전체연관연구, 가족기반연관연구, 유전자 별 성격의 상호작용, 건강 행동, 맞춤 의학

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