

# Molecular Genetics of Human Personality Traits for Psychiatric, Behavioral, and Substance-Related Disorders

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**Abstract:** The investigation of personality genetics had received much attention since the three seminal reports showing an association between genes and personality traits in the general population. Accumulating evidences suggested that personality traits have significant genetic components. Although currently available data are not enough for proof, more and more genetic variants associated with personality traits are being discovered. In this paper, we review related studies of gene polymorphisms and human personality traits for psychiatric, behavioral, and substance-related disorders. First, we briefly describe the commonly-used self-reported temperament measures that define personality dimensions. Then, we summarize the characteristics of the candidate genes for personality traits, and investigate gene variants which have been suggested to be linked with personality traits for individuals with psychiatric, behavioral, and substance-related disorders.

**Keywords:** Molecular genetics, personality, psychiatric disorders, temperament measures.

## 1. INTRODUCTION

The investigation of personality genetics had received much attention since the three seminal reports [1-3] in 1996 showing an association between genes and personality traits in the general population. Accumulating evidences suggested that personality traits have significant genetic components [4-7]. Although currently available data are not enough for proof, more and more genetic variants associated with personality traits are being discovered [4-7]. Personality traits can be measured by several self-reported questionnaires including the Tridimensional Personality Questionnaire (TPQ) [8], the Temperament and Character Inventory (TCI) [9], the Revised NEO Personality Inventory (NEO-PI-R) [10], the Eysenck Personality Questionnaire (EPQ) [11,12], and the Zuckerman-Kuhlman Personality Questionnaire (ZKQP) [13].

Related studies have identified the serotonin transporter gene (SLC6A4) polymorphisms as genetic markers that are correlated with personality traits, such as NEO-PI-R neuroticism and TCI harm avoidance [14-16]. A common SLC6A4 gene polymorphism is the serotonin transporter gene-linked polymorphic region (5-HTTLPR) variant. A recent meta-analysis observed a significant association between 5-HTTLPR and NEO-PI-R neuroticism, but not with TCI/TPQ harm avoidance or EPQ neuroticism [16]. This result was consistent with previous reports which indicated that there was evidence of association between NEO-PI-R neuroticism

and 5-HTTLPR but not other anxiety-related personality traits [14,15].

We reviewed related studies of gene polymorphisms and human personality traits for psychiatric, behavioral, and substance-related disorders. First, we briefly describe the commonly-used self-reported temperament measures that define personality dimensions. Then, we summarize the characteristics of the candidate genes for personality traits, and investigate gene variants which have been suggested associated with personality traits for individuals with psychiatric, behavioral, and substance-related disorders, including alcoholism, anxiety-depression alcoholism, antisocial personality disorder with alcoholism, borderline personality disorder, binge eating disorder, bulimia nervosa, internet addiction, mood disorders, and nicotine dependence. One of the intentions of these previous studies was that our knowledge of the genetics of personality may enhance our understanding of the genetic basis of psychiatric, behavioral, and substance-related disorders. Moreover, examination of subjects in specific populations with these disorders may improve our understanding of the genetic basis of personality in the general population.

## 2. SELF-REPORTED TEMPERAMENT MEASURES

### 2.1. Tridimensional Personality Questionnaire (TPQ)

Based on a general biosocial theory of personality, Cloninger proposed that the TPQ defines three dimensions of personality in terms of the basic stimulus-response characteristics of novelty seeking, harm avoidance, and reward dependence [8]. Novelty seeking tends to be associated with low basal dopaminergic activity and is related to a tendency toward exploratory behavior in search of novel stimuli, impulsive responding, and extravagance in approach to cues of reward [9,17]. Harm avoidance tends to be associated with

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high serotonergic activity and involves a tendency to over-respond to aversive stimuli, worry about future problems, fear uncertainty, and act shy around strangers [9,18]. Reward dependence tends to be associated with low noradrenergic activity and is characterized by a tendency toward sentimentality, social sensitivity, attachment, and dependence on approval by others [9,19].

## 2.2. Temperament and Character Inventory (TCI)

The TPQ is subsequently evolved into the TCI which describes a self-reported measure of seven personality dimensions, including four dimensions of temperament (novelty seeking, harm avoidance, reward dependence and persistence) and three dimensions of character (self-directedness, cooperativeness, self-transcendence) [9]. The TCI has 226 items and has an abbreviated version that employs a true-false format with 125 items.

## 2.3. Revised NEO Personality Inventory (NEO-PI-R)

The NEO-PI-R is a 240-question measure of the Five Factor Model: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness [10]. Traits in the neuroticism domain describe different ways of reacting emotionally to distressing circumstances. The extraversion domain is concerned with energy and enthusiasm. The facets of the openness to experience domain are associated with intellectual curiosity and aesthetic sensitivity. The agreeableness domain measures traits related to styles of interpersonal interaction. Traits in the conscientiousness domain reflect differences in motivation and persistence.

A study showed that The TPQ/TCI significantly correlated with the NEO-PI-R [20], demonstrating that TPQ/TCI novelty seeking is correlated to NEO-PI-R extraversion and openness to experience and negatively to conscientiousness. Furthermore, TPQ/TCI harm avoidance is strongly related positively with NEO-PI-R neuroticism and negatively to extraversion. In addition, TPQ/TCI reward dependence is primarily correlated with NEO-PI-R extraversion and secondarily with openness to experience. Finally, TPQ/TCI persistence is highly related to conscientiousness.

## 2.4. Eysenck Personality Questionnaire (EPQ)

The EPQ conceptualizes personality as three categories of temperament: extraversion (impulsiveness and sociability), psychoticism (vulnerability to psychoses) and neuroticism (emotional instability) [11,12]. The EPQ has 100 items and has a 48-item short scale questionnaire.

A study suggested that TPQ/TCI harm avoidance represents a 45 degree rotation of EPQ extraversion and neuroticism most likely [21]. Moreover, TPQ/TCI novelty seeking appears to be further rotated into EPQ psychoticism space. However, TPQ/TCI reward dependence is not equivalent to EPQ psychoticism, showing that TPQ/TCI reward dependence is negatively related with EPQ psychoticism modestly.

## 2.5. Zuckerman-Kuhlman Personality Questionnaire (ZKPQ)

In order to narrow the scope of study on risk-taking and personality, the ZKPQ assesses personality along for five dimensions, including impulsive sensation seeking (which has two subscales: impulsivity and sensation seeking), neu-

roticism-anxiety, aggression-hostility, activity (formed by two subscales: work effort and general activity), and sociability (made up of two subscales: isolation intolerance and liking of parties and friends) [13]. The ZKPQ is an 89-item self-reported measure and is an extension of the EPQ three dimensions of personality.

## 3. PERSONALITY GENETICS FOR PSYCHIATRIC DISORDERS

In this paper, we review the following candidate genes that may be strongly associated with personality traits for psychiatric, behavioral, and substance-related disorders: dopamine D2 receptor (DRD2), dopamine D4 receptor (DRD4), 5-hydroxytryptamine receptor 2A (HTR2A; serotonin receptor 2A), monoamine oxidase A (MAOA), SLC6A4, and tryptophan hydroxylase 1 (TPH1).

### 3.1. Dopamine Receptors

Dopamine receptors play a key role in many processes, including motor behavior, motivation, and working memory [22]. DRD2 and DRD4 receptors are subtypes of dopamine receptors, and their common gene polymorphisms are DRD2 TaqIA polymorphism and DRD4 exon III polymorphism, respectively. Evidence showed that they contribute to personality traits in the general population [7].

#### 3.1.1. Anxiety-Depression Alcoholism

In a study of Lin and colleagues, they investigated a Taiwanese population of 87 anxiety-depression alcohol dependents and 46 pure alcohol dependents, to see whether the TaqIA polymorphism of the DRD2 gene is involved in TPQ novelty seeking and harm avoidance [23]. DRD2 TaqI A1(+) allele (A1/A1 or A1/A2 genotypes) was found to be associated with TPQ novelty seeking in anxiety-depression alcohol dependents [23].

Anxiety-depression alcohol dependence was defined as a genetically specific subtype of alcoholism [24]. Four homogeneous types of alcoholism have been suggested, including the depressed/anxious type, the chronic/severe type, the mildly affected type and the antisocial type [25]. Anxiety disorders represent one of the most common mental illnesses and are complex diseases with both genetic and environmental factors affecting their predisposition [26]. Recent data revealed that the genetic variant of the DRD2 gene was associated with anxiety-depression alcohol dependence [27].

#### 3.1.2. Antisocial Personality Disorder with Alcoholism

In a Taiwanese population of antisocial personality disorder, 43 with alcoholism and 84 without alcoholism, Wu and colleagues examined the DRD2 gene and the SLC6A4 5-HTTLPR variant on TPQ novelty seeking [28]. They found evidence for an interaction between DRD2 TaqI A1+ (including A1/A1 or A1/A2) and 5-HTTLPR short/short genotype in the novelty seeking scores, and found significant difference in 5-HTTLPR polymorphisms between antisocial alcoholics and antisocial non-alcoholics after stratification of DRD2 TaqIA genotypes [28].

Antisocial personality disorder is a mental disorder defined by a pervasive pattern of deception, manipulation, disregard for the rights of others, and a lack of remorse for their behavior that begins in childhood or early adolescence [29].

Genetic studies showed evidence of genetic influences on personality disorder, such as antisocial personality disorders, borderline personality disorders, schizotypal personality disorders [30-32]. A recent study suggested that the possible interactions between the MAOA and DRD2 genes might be related to antisocial personality disorder with alcoholism among Taiwanese [33]. Future research should further investigate the contributions of the MAOA gene to personality traits in antisocial personality disorder with alcoholism.

### 3.1.3. Binge Eating Disorder

Davis and colleagues compared participants with binge eating disorder ( $n = 56$ ) to normal-weight ( $n = 59$ ) and obese controls ( $n = 51$ ) on reward sensitivity and genotyped six markers (TaqIA, -141C Ins/Del, -241A/G, Taq1D, C957T, and rs4648317) of the DRD2 dopamine receptor gene [34]. Two personality measures of reward sensitivity were employed, including the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scales [35] and the Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) [36]. They reported that binge eating disorder and obese participants had greater reward sensitivity than normal-weight controls, but only among those carrying the A1 allele of the TaqIA marker [34].

Binge eating disorder is a provisional eating disorder diagnosis, which core symptom is recurrent binge eating [37,38], and the episode requires consumption of an unusually large amount of food and a sense of being out of control. In addition, individuals with binge eating disorder do not regularly engage in compensatory behaviors. Recent studies suggested that the 5-HTTLPR [39] and ghrelin/obestatin prepropeptide (GHRL) [40] may contribute to the genetic susceptibility to the disorder. Future research should further investigate the contributions of the SLC6A4 and GHRL genes to personality traits in binge eating disorder.

### 3.1.4. Mood Disorders

In a study of 73 major depressive disorder and 134 bipolar disorder patients, Serretti and colleagues tested the hypothesis that the exon III variant in the DRD4 gene could influence personality traits in the patients of mood disorders [41]. Genotypes with the long repeat of DRD4 exon III polymorphism were marginally associated with low TCI harm avoidance [41].

Depression and bipolar disorder are the two major types of mood disorders, in which the emotional mood of a patient is distorted or inappropriate to the circumstances [42]. Owing to the fact that personality is itself a complex trait, its use as an endophenotype for genetic studies of bipolar disorder has certain limitations [43]. Newer hypotheses of depression neurobiology suggest an association of major depressive disorder with polymorphisms in the brain-derived neurotrophic factor (BDNF) gene [44]. Future research should further study the contributions of the BDNF gene to personality traits in major depressive disorder.

## 3.2. HTR2A

Serotonin receptors are receptors for the neurotransmitter serotonin, which is also known as 5-hydroxytryptamine. HTR2A receptors are a subtype of serotonin receptors and play an important role in embryogenesis and in the periphery [45]. It was reported that there was a credible association

between the HTR2A gene and personality traits in the general population [7].

### 3.2.1. Borderline Personality Disorder

Based on a Caucasian sample of 111 patients with borderline personality disorder and 287 healthy controls, Ni and colleagues tested the association between the HTR2A gene and personality traits in borderline personality disorder [46]. Among four polymorphisms (rs6313, rs4941573, rs2296972, and rs6314) of the HTR2A gene, the C allele of rs6313 and the A allele of rs4941573 were found to be associated with a higher NEO-PI-R extraversion score, indicating that there were significant associations between the HTR2A gene and personality traits in the patients with borderline personality disorders [46].

Borderline personality disorder, which begins in early adulthood, is a chronic and severe mental disorder characterized by a pervasive pattern of instability in affect regulation, interpersonal relationships, self-image, and impulse control [47]. The SLC6A4 and MAOA genes have been suggested to be involved in the development of it [48]. A recent study demonstrated that there were gender differences in TCI novelty seeking in borderline personality disorder [49]. In future work, the contributions of the MAOA gene to personality traits in borderline personality disorder should be further investigated.

## 3.3. MAOA

The MAOA gene is located on the short arm of the X chromosome and encodes the MAOA enzyme that degrades amine neurotransmitters such as dopamine, norepinephrine, and serotonin [50]. The functional MAOA-upstream variable number of tandem repeats (MAOA-uVNTR) polymorphism in the MAOA gene promoter commonly consists of 3 (3-allele) or 4 (4-allele) copies of a 30-bp sequence, or rarely 2 (2-allele) or 3 copies plus the first 18-bp of the same 30-bp sequence (3a-allele), or 5 copies (5-allele). It was suggested that the MAOA gene was found to be associated with personality traits in the general population [7].

### 3.3.1. Mood Disorders

Serretti and colleagues [41] tested the uVNTR variant in the MAOA gene to see if it influences personality traits in the patients of mood disorders or not. The long MAOA allele was found to be associated with decreased TCI persistence scores among female patients [41].

## 3.4. SLC6A4

The SLC6A4 gene encodes an integral membrane protein that transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons, terminates the action of serotonin, and recycles it into the neurotransmitter pool [51]. The common SLC6A4 gene polymorphisms are the short and long alleles of the 5-HTTLPR variant and alleles of the variable number tandem repeats (VNTR) region in the second intron. There are three possible alleles of VNTR, including 9 repeats (345 bp), 10 repeats (360 bp), and 12 repeats (390 bp), and the possible genotypic combinations are as follows: 9/10, 9/12, 10/10, 10/12 and 12/12. Anxiety-related personality traits, mood disorders, antidepressants response, alcoholism, smoking, and eating disorders have been found to be related to the SLC6A4 variants [52,53].

### 3.4.1. Alcoholism

In a study on German alcohol dependents ( $n = 368$ ), Koller and colleagues [54] hypothesized that the 5-HTTLPR and VNTR variants of the SLC6A4 gene are associated with TCI harm avoidance. An association between short/12-repeat haplotype of SLC6A4 and low level of TCI harm avoidance was found [54]. Furthermore, no significant association was found between TCI harm avoidance and the SLC6A4 5-HTTLPR variant as well as between TCI harm avoidance and the SLC6A4 VNTR variant [54].

Conversely, in a study of 124 subjects seeking inpatient treatment for primary alcohol dependence, Wiesbeck and colleagues reported that the SLC6A4 5-HTTLPR variant was associated with TCI harm avoidance in the group [55]. The conflicting results between this work and the report [54] by Koller and colleagues may be due to the differences in sample sizes, different ethnicities, or different study designs. The studies conducted on small patient populations may also have biased a particular result.

Alcoholism is a chronic disease characterized by alcohol abuse despite recurrent adverse consequences [56]. Recent evidence supports genetic associations with alcoholism of the glutamate receptor ionotropic N-methyl D-aspartate 2A (GRIN2A) gene [57] and MAOA genes [27]. In future work, the contributions of the GRIN2A and MAOA genes to personality traits in alcohol dependence should be further tested.

### 3.4.2. Anxiety-Depression Alcoholism

Lin and colleagues [23] assessed whether the SLC6A4 5-HTTLPR variant is involved in TPQ novelty seeking and harm avoidance, and found that the short/short genotype of the SLC6A4 5-HTTLPR variant was associated with TPQ novelty seeking in anxiety-depression alcohol dependents [23].

### 3.4.3. Borderline Personality Disorder

Pascual and colleagues investigated the association between the SLC6A4 5-HTTLPR and VNTR polymorphisms and personality traits in their study of 65 patients with borderline personality disorder [58]. They reported that patients with long allele (long/short or long/long) in the 5-HTTLPR polymorphism of the SLC6A4 gene showed lower scores on the subscale of the ZKPQ liking of parties and friends [58]. Furthermore, patients with the allele with 10 repeat of the SLC6A4 VNTR polymorphism were found to show lower scores in the ZKPQ impulsivity, sensation seeking and in the subscale liking of parties and friends [58].

### 3.4.4. Bulimia Nervosa

Monteleone and colleagues [59] tested whether the 5-HTTLPR polymorphism of the SLC6A4 gene is related to TCI harm avoidance or not. In 125 female Caucasian patients with bulimia nervosa and 94 healthy controls, they found that patients with bulimia nervosa carrying at least one copy of the short allele have significantly higher mean TCI harm avoidance score than those with the long/long genotype [59].

The TPH1 gene codes for tryptophan hydroxylase, the rate-determining enzyme in serotonin biosynthesis [60]. Likewise, Monteleone and colleagues [61] tested whether A218C polymorphism of the TPH1 gene is related to TCI

harm avoidance. In their study of 180 female Caucasians (91 patients with bulimia nervosa and 89 healthy controls), they demonstrated that bulimic women with the AA genotype of the TPH1 gene exhibited a more severe binge eating behavior and higher TCI harm avoidance scores than those with CC genotype [61]. Together with the similar study [59] previously discussed, the findings of these two studies support the idea that the SLC6A4 5-HTTLPR polymorphism and the TPH1 A218C polymorphism are involved in predisposing bulimic patients to a more disturbed eating behavior and higher TCI harm avoidance [59,61].

Bulimia nervosa is an eating disorder characterized by recurrent binge eating, which is followed by compensatory behaviors, such as self-induced vomiting, fasting, and over-exercising [38,62]. A recent study revealed that the GHRL gene is associated with susceptibility to bulimia nervosa [63]. In future work, the contributions of the GHRL gene to personality traits in bulimia nervosa should be further assessed.

### 3.4.5. Internet Addiction

Internet addiction or excessive internet use is defined as uncontrollable and damaging use of the internet and has been compared to other addictions such as pathological gambling [64]. In a Korean population of 91 male adolescents with excessive internet use and 75 healthy controls, Lee and colleagues conducted group comparisons on the 5-HTTLPR polymorphism of the SLC6A4 gene with respect to TCI novelty seeking and harm avoidance [65]. It was found that participants with excessive internet use with 5-HTTLPR short/short genotype showed higher TCI harm avoidance scores than the ones with the other allele variants [65].

### 3.4.6. Mood Disorders

Serretti and colleagues [41] further tested the hypothesis that the variants in the SLC6A4 gene could influence personality traits in the patients of mood disorders. It was observed that the 5-HTTLPR short/short genotype frequency was associated with low TCI novelty seeking scores [41].

Furthermore, based on a sample of 251 participants, another study observed that EPQ neuroticism mediates the association between the SLC6A4 5-HTTLPR polymorphism and lifetime major depression [66].

### 3.4.7. Nicotine Dependence

Nicotine dependence is the physical vulnerability of human body to the chemical nicotine, which is a psychoactive ingredient in tobacco significantly contributing to the harmful tobacco smoking habit [67]. In a study of personality genetics, Kremer and colleagues recruited 244 smokers and examined the association of smoking with the 5-HTTLPR and VNTR polymorphisms of the SLC6A4 gene [68]. It was observed that there was a weak association between TPQ novelty seeking and the VNTR polymorphism as well as between TPQ reward dependence and the 5-HTTLPR polymorphism [68].

Recent studies have reported genetic associations with nicotine dependence of the following genes: BDNF [69,70], cholinergic receptor nicotinic alpha 4 (CHRNA4) [71-73], cannabinoid receptor 1 (CNR1) [74], neurexin 1 (NRXN1) [75], and neurotrophic tyrosine kinase receptor type 2

**Table 1. Candidate Genes Associated with Personality Traits for Psychiatric, Behavioral, and Substance-Related Disorders**

Gene	Polymorphisms	Personality Traits	Phenotype	Results	Reference
DRD2	TaqIA	TPQ novelty seeking	Anxiety-depression Alcoholism	Associated with TPQ novelty seeking	[23]
	TaqIA	TPQ novelty seeking	Antisocial personality disorder with alcoholism	An interaction between DRD2 TaqI A1+ (including A1/A1 or A1/A2) and 5-HTTLPR short/short genotype in TPQ novelty seeking	[28]
	TaqIA	BIS/BAS and SPSRQ reward sensitivity	Binge eating disorder	Having greater reward sensitivity than normal-weight controls, but only among those carrying the A1 allele	[34]
DRD4	exon III	TCI harm avoidance	Mood disorders	Genotypes with the DRD4 long allele marginally associated with low TCI harm avoidance	[41]
HTR2A	rs6313, rs4941573	NEO-PI-R extraversion	Borderline personality disorder	The C allele of rs6313 and the A allele of rs4941573 associated with a higher extraversion score	[46]
MAOA	uVNTR	TCI persistence	Mood disorders	The long MAOA allele associated with decreased TCI persistence scores among female patients	[41]
SLC6A4	5-HTTLPR/ VNTR	TCI harm avoidance	Alcoholism	Association between short/12-repeat haplotype of SLC6A4 and low level of TCI harm avoidance	[54]
	5-HTTLPR	TCI harm avoidance	Alcoholism	Associated with TCI harm avoidance	[55]
	5-HTTLPR	TPQ novelty seeking	Anxiety-depression Alcoholism	The 5-HTTLPR short/short genotype associated with TPQ novelty seeking	[23]
	5-HTTLPR	ZKPQ liking of parties and friends	Borderline personality disorder	The long allele (long/short or long/long) in 5-HTTLPR showed lower scores on the subscale of the ZKPQ liking of parties and friends	[58]
	5-HTTLPR	TCI harm avoidance	Bulimia nervosa	The short allele (short/short or short/long) in 5-HTTLPR had significantly higher mean TCI harm avoidance score	[59]
	5-HTTLPR	TCI harm avoidance	Internet addiction	The 5-HTTLPR short/short genotype showed higher TCI harm avoidance scores	[65]
	5-HTTLPR	TCI novelty seeking	Mood disorders	The 5-HTTLPR short/short genotype associated with low TCI novelty seeking score	[41]
	5-HTTLPR	TPQ reward dependence	Nicotine dependence	A weak association between TPQ reward dependence and 5-HTTLPR	[68]
	VNTR	ZKPQ impulsivity, sensation seeking, and liking of parties and friends	Borderline personality disorder	The allele with 10 repeat of SLC6A4 VNTR showed lower scores in the ZKPQ impulsivity, sensation seeking and in the subscale liking of parties and friends	[58]
	VNTR	TPQ novelty seeking	Nicotine dependence	A weak association between TPQ novelty seeking and SLC6A4 VNTR	[68]
TPH1	A218C	TCI harm avoidance	Bulimia nervosa	Bulimic women with the TPH1 AA genotype exhibited a more severe binge eating behavior and higher TCI harm avoidance scores than those with CC genotype	[61]

The "rs number" means the NCBI SNP ID.

5-HTTLPR, serotonin transporter gene-linked polymorphic region; BIS/BAS, Behavioral Inhibition System/Behavioral Activation System; DRD2, dopamine D2 receptor; DRD4, dopamine D4 receptor; HTR2A, 5-hydroxytryptamine receptor 2A (serotonin receptor 2A); MAOA, monoamine oxidase A; NEO-PI-R, Revised NEO Personality Inventory; SLC6A4, solute carrier family 6 member 4 (serotonin transporter); SPSRQ, Sensitivity to Punishment and Sensitivity to Reward Questionnaire; TCI, Temperament and Character Inventory; TPH1, tryptophan hydroxylase 1; uVNTR, the upstream variable number of tandem repeats in the MAOA gene promoter; VNTR, the variable number tandem repeats region in the second intron of the SLC6A4 gene; TPQ, Tridimensional Personality Questionnaire; ZKPQ, Zuckerman-Kuhlman Personality Questionnaire.

(NTRK2) [76]. In future work, the contributions of these genes to personality traits in nicotine dependence should be further examined.

#### 4. CONCLUSIONS

Table 1 summarizes the candidate genes associated with personality traits for psychiatric, behavioral, and substance-related disorders as described in this article. This is by no means a comprehensive review of all potential markers reported in the literature. As mentioned previously, increasing numbers of markers are being identified as researchers continue to pay attention to personality genetics. As shown in Table 1, the 5-HTTLPR polymorphism of the SLC6A4 gene was found to be related to TCI harm avoidance for alcoholism, bulimia nervosa, and internet addiction [55,59,65]. Moreover, the SLC6A4 5-HTTLPR polymorphism was suggested to be linked to TPQ/TCI novelty seeking with anxiety-depression alcoholism and mood disorders [23,41]. In anxiety-depression alcoholism, it was also indicated that the DRD2 TaqIA and SLC6A4 5-HTTLPR polymorphisms were associated with TPQ novelty seeking [23]. In addition, the SLC6A4 and TPH1 genes seem to be involved in predisposing patients with bulimia nervosa to higher TCI harm avoidance [59,61]. Furthermore, the SLC6A4 and HTR2A genes may play a role in personality traits with borderline personality disorder [46,58]. By examining subjects in specific populations with psychiatric, behavioral, and substance-related disorders and testing association between candidate genes in these groups, these studies provide a favorable approach to solve the complexity problems of personality genetics [7].

With respect to the previously discussed association studies in the personality genetic study, several limitations include issues such as small effect sizes, polygenic inheritance, environmental influences, the constraints of self-report questionnaires, generalizability, population stratification, multi-ethnicity, studies without genome-wide association and considering gene-gene and gene-environment interactions [7].

In future work, it will be indispensably necessary to identify a panel of candidate genes that are reproducibly associated with personality traits for psychiatric, behavioral, and substance-related disorders. At this point, no genetic markers listed in the previous studies would really qualify to enter the panel due to the limitations as described above. There are several selection criteria for genetic markers to enter such a panel. One is independent replications in genome-wide association studies to confirm associations. It is now technically and financially feasible to conduct genome-wide association studies using dense genotyping chips [77,78]. Moreover, a multistage approach with independent samples is needed to replicate findings [77]. Finally, pattern recognition techniques such as the artificial neural network approach may provide a plausible way to assess gene-gene and gene-environment interactions [79-81].

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