

Trends and Directions in Personality Genetic Studies

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Abstract

How personality forms and whether personality genes exist are long-studied questions. Various concepts and theories have been presented for centuries. Personality is a complex trait and is developed through the interaction of genes and the environment. Twin and family studies have found that there are critical genetic and environmental components in the inheritance of personality traits, and modern advances in genetics are making it possible to identify specific variants for personality traits. Although genes that were found in studies on personality have not provided replicable association between genetic and personality variability, more and more genetic variants associated with personality traits are being discovered. Here, we present the current state of the art on genetic research in the personality field and finally list several of the recently published research highlights. First, we briefly describe the commonly used self-reported measures that define personality traits. Then, we summarize the characteristics of the candidate genes for personality traits and investigate gene variants that have been suggested to be associated with personality traits.

Keywords: personality gene, NEO-PI, TCI, TPQ, EPQ

Introduction

The modern tools for the assessment of personality have been developed in the last half century. Personality traits can be measured by several self-reported questionnaires, including the Eysenck Personality Questionnaire (EPQ) (Eysenck *et al.*, 1975), the Sixteen Personality Factor Questionnaire (16PF) (Cattell *et al.*, 1970), the Revised NEO Personality Inventory (NEO-PI-R) (Costa *et al.*, 1992; Costa *et al.*, 1997), the Temperament and Character Inventory (TCI) (Cloninger *et al.*, 1993), and the Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987). Most personality theories and instruments

have large overlaps with concepts contained in the five-factor model using NEO-PI-R.

Twin, adoption, and family studies have demonstrated the importance of genetic influences on personality. In a twin study, the heritability estimates for the NEO (five-factor model) personality traits reached between 40~60% (Bouchard *et al.*, 2001). Almost identical results have been reported for the TCI temperament. Furthermore, the shared environment makes very little contribution, and the nonshared environment is the largest contributor for all personality traits (Matthews *et al.*, 2009). In adoption studies, the heritability estimates were reported to be lower than those from twin studies, possibly because nonadditive genetic factors may play a role in personality (Bouchard *et al.*, 2001).

The relative influences of genetic and environmental factors in the development of human personality have been a long-term topic for an intense debate. The studies of personality genetics began with the simultaneous publication of two articles in 1996, showing an association between Novelty Seeking and the D4 dopamine receptor gene (Benjamin *et al.*, 1996; Ebstein *et al.*, 1996). This discovery was quickly followed by a report suggesting that activity of the serotonin transporter protein (SERT) affects the development of anxiety-related traits (Lesch *et al.*, 1996). The continuing series urged by these reports, however, have resulted in both successful and unsuccessful replication of these first studies. Although currently available data are not enough for proof, the search for personality genes is being continued.

In the present study, we briefly describe the commonly used self-reported measures that define personality traits. Then, we summarize the characteristics of the candidate genes for personality traits and investigate gene variants that have been suggested to be associated with personality traits for individuals with behavioral outcomes and other psychiatric disorders. The purpose of this review is to improve our understanding of the genetic basis of personality.

Self-Reported Personality Measures

Modern personality research focuses primarily on personality trait dimensions of variation between individuals who are relatively stable over time and predict behavior in various domains (Verweij *et al.*, 2010). According to the personality theory of Eysenck, there are three broad personality factors, named Neuroticism, Extraversion-

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Introversion, and Psychoticism (Eysenck, 1967). The Eysenck Personality Questionnaire (EPQ) has 100 items and has a 48-item short-scale questionnaire. Eysenck's contributions to personality research was his formulation of theories of the biological bases of his personality dimensions (Eysenck, 1967). Cattell *et al.* (1970) used a lexical approach by searching clusters of traits in the adjectives people use to describe an individual's personality and found 16 factors, which can be measured by the Sixteen Personality Factor Questionnaire (16PF). Using the same method, several researchers found five robust factors. The Revised NEO Personality Inventory (NEO-PI-R) is questionnaire designed to measure the Five-Factor Model (FFM) of the so-called "Big Five" dimensions of personality (De Raad, 2000). Full NEO-PI-R is a 240-item or shorter scale. Costa and McCrae set the most widely used terminology as Neuroticism, Extraversion, Conscientiousness, Openness, and Agreeableness (Costa *et al.*, 1992). Neuroticism includes traits, such as anxiety, depression, and self-confidence. Extraversion includes traits, such as energy and optimism. The FFM reported evidence of cross-cultural similarities in the structure, sex differences, and age trajectories of the five factors and asserted that the five factors are a human universal, with the traits being primarily genetically influenced (McCrae *et al.*, 2005).

An alternative model, developed by Cloninger, aims to reflect the psychobiological etiology of personality (Cloninger, 1986; Cloninger, 1987). Cloninger's model originally consisted of three dimensions of personality (temperaments): Novelty Seeking, Harm Avoidance, and Reward Dependence, measured by the Tridimensional Personality Questionnaire (TPQ; Cloninger, 1986; Cloninger *et al.*, 1991). The Temperament and Character Inventory (TCI) is a revised model of TPQ including an additional characteristic, Persistence. As Cloninger predicted, scores on certain TPQ/TCI scales are associated with specific problem behaviors and psychological disorders, including depression, anxiety, bipolar disorder, obsessive compulsive disorder, conduct disorder, alcohol and drug dependence, criminal behavior, and anti-social personality disorder (Khan *et al.*, 2005; Nery *et al.*, 2009; Ongur *et al.*, 2005). The TCI has 226 items and has a short version of 125 items.

A study showed that TPQ/TCI scales significantly correlated with the NEO-PI-R domain scale, demonstrating that each TPQ/TCI scale has overlap with the NEO-PI-R scale (De Fruyt *et al.*, 2000). Stallings *et al.* suggested that TPQ/TCI Harm Avoidance represents a 45 degree rotation of EPQ Extraversion and Neuroticism most likely (Stallings *et al.*, 1996). In general, there is a reasonable degree of congruence between the five-factor model and personality factors from a wide range of schemes

devised by different authors with different theoretical orientations; that is, no matter what the actual traits are named in other questionnaires, they tend substantially to assess some or all of the traits of the FFM (Matthews *et al.*, 2009).

Candidate Gene Approach

In molecular genetic studies of personality, a frequently used design is the candidate gene approach. Since processes in the brain were assumed to regulate personality, genes involved in neurotransmitter pathways were primary candidates (Van Gestel and Van Broeckhoven, 2003). In the psychobiological model of personality, personality were hypothesized to be linked to the neurotransmitter systems, which are serotonin, dopamine, and noradrenaline (Cloninger, 1987). These theoretical assumptions led several researchers to examine genes from these specific neurotransmitter pathways.

Serotonin

The serotonin transporter (SERT) gene (also called 5-hydroxytryptamine, or 5HT) encodes an integral membrane protein that transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons. Two SERT polymorphisms have been used in association analyses. This genetic variation is said to occur in the 5-HT transporter-linked polymorphic region (5-HTTLPR) (Deary *et al.*, 1999). The short allele(s) was associated with higher neuroticism levels in a study of 505 subjects, whether measured by the NEO-PI-R or Cattell's 16PF (Goldman, 1996; Lesch *et al.*, 1996). The allele was also associated with anxiety, angry hostility, depression, and impulsiveness facets of NEO-PI Neuroticism and with scores for the TPQ Harm Avoidance trait. Attempts to replicate the association had mixed results, with some studies confirming the finding (Greenberg *et al.*, 2000; Katsuragi *et al.*, 1999; Murakami *et al.*, 1999) and some not (Ebstein *et al.*, 1997a; Flory *et al.*, 1999; Gustavsson *et al.*, 1999).

The second extensively studied polymorphism is a 17-bp variable number tandem repeat (VNTR) in the second intron of the 5-HTT gene. Three alleles with 9, 10, and 12 repeats, respectively, have been characterized. Initially there was no evidence that the polymorphism influenced gene expression (Gelernter *et al.*, 1998), but more recent studies have suggested that the VNTR is associated with scores on the Harm Avoidance trait subscale, measuring fear of uncertainty versus confidence (Tsai *et al.*, 2002).

Recently, a functional magnetic resonance imaging

study supported the genetic variability of this site being involved in emotion-based personality differences. The individuals with the short allele of 5-HTTLPR showed greater activity in the right amygdala in response to fear-related stimuli (Ebstein *et al.*, 1997a; Hariri *et al.*, 2002).

Two other genes from the serotonin pathway were studied in relation to personality: the serotonin receptor 2A (5-HTR2A) and the serotonin receptor 2C (5-HT2C) genes. The associations between 5-HTR2A and relevant scores on the TCI questionnaire were evaluated. Effects of a 5-HTR2A gene marker and its interaction with the GABRA6 gene on Harm Avoidance were detected (Alfimova *et al.*, 2010). A polymorphism of 5-HT2C was associated with the TPQ dimensions Reward Dependence, and in addition, a significant interaction effect of DRD4 and 5-HT2C on Reward Dependence was detected (Ebstein *et al.*, 1997b). However, a recent study in the Japanese population did not provide evidence for the association between 5-HT2C and NEO-PI-R scores (Tochigi *et al.*, 2006).

Dopamine

Dopamine receptors play a key role in many processes, including motor behavior, motivation, and working memory (Girault *et al.*, 2004). DRD2 and DRD4 receptors are subtypes of dopamine receptors, and their common gene polymorphisms are the DRD2 TaqI A polymorphism and VNTR of DRD4 exon III, respectively. A significant association was reported between TPQ Novelty Seeking tendencies and variations in the DRD4 gene (Cloninger *et al.*, 1996). This association was replicated across several studies using the TPQ and NEO-PI-R (Benjamin *et al.*, 1996; Tochigi *et al.*, 2006), while in others, no effect could be demonstrated in the healthy population or in patients (Gelernter *et al.*, 1997; Sander *et al.*, 1997; Sullivan *et al.*, 1998). One study that included 616 healthy Japanese subjects reported no significant associations between the DRD4 VNTR polymorphism and any TCI score (Tsuchimine *et al.*, 2009). The TaqI A polymorphism of the DRD2 gene is involved in TPQ Novelty Seeking and Harm Avoidance in anxiety-depression alcohol dependents (Huang *et al.*, 2007; Lin *et al.*, 2007). Since then, a number of researchers have examined the relationship between DRD2 polymorphisms and personality traits, with mixed results.

Other Genes of Interest

Other genes implicated in personality development include the MAOA enzyme (Soliman *et al.*, 2011; Urata *et al.*, 2007), GABRA6 (Alfimova *et al.*, 2010), BDNF (Suzu-

ki *et al.*, 2011; Terracciano *et al.*, 2010a), and COMT (Tochigi *et al.*, 2006; Urata *et al.*, 2007). Unfortunately, negative reports are ubiquitous (Jorm *et al.*, 2000; Lee *et al.*, 2008).

Genome-wide Linkage Study

The first genome-wide scan for personality was carried out by Cloninger *et al.* (1998). A total of 758 sib pairs from 177 nuclear families of alcoholics were tested using the TPQ. The significant linkage was observed between Harm Avoidance and a region on chromosome 8p21-23, explaining a considerable fraction of the trait variance. The significant evidence of epistasis was also observed with loci on 18p, 20p, and 21q, and oligogenic interactions explained most of the variance in this personality trait. The linkage of Harm Avoidance to 8p21 was replicated in an independent sample (Zohar *et al.*, 2003).

The genome-wide scan by Fullerton *et al.* (Fullerton *et al.*, 2003), which used an extremely concordant-discordant sibling design, screened a large UK population for subjects at the phenotypic extreme of the EPQ-R Neuroticism scale. Linkage was observed on 1q, 4q, 7p, 12q, and 13q, which met or exceeded the 5% genome-wide significance. Weaker evidence for linkage on 8p and on 11q was reported, but this is of considerable interest, since 8p and 11q overlap with regions reported in the Cloninger study.

In Dutch and Australian populations, extremely concordant and discordant sibling and twin pairs were tested for genome-wide linkage for several personality traits (Boomsma *et al.*, 2000; Kirk *et al.*, 2000). Recently, Gillespie *et al.* (Gillespie *et al.*, 2008) reported the genome-wide scan for Eysenck Personality Dimensions in adolescent twin sibships. The highest linkage peaks were found on chromosomes 16 and 19 for Neuroticism; on chromosomes 1, 7, 10, 13 m, and 18 for Psychoticism; and on chromosomes 2 and 3 for Extraversion.

Genome-wide Association Study (GWAS)

The genome-wide association studies have already scored successes in several illnesses, such as type 2 diabetes (Frayling, 2007), and quantitative traits, such as height (Visscher, 2008). An early genome-wide association study of neuroticism (based on pools of DNA with high and low Neuroticism scores rather than on individuals) found nothing that was consistently replicable (Shifman *et al.*, 2008). The authors concluded that the heritability of neuroticism probably arises from many loci, each explaining much less than 1% of the phenotypic variation. No significant SNPs were identified un-

der linkage peaks derived from sib pairs in the same cohort (Fullerton *et al.*, 2003; Martin *et al.*, 2000). They reported an association in the PDE4D, but the result was not genome-wide significant. Recently, Calboli *et al.* performed a GWAS for EPQ Neuroticism, but they could not find common SNP variations strongly influencing neuroticism (Calboli *et al.*, 2010).

Gene-finding studies for personality, including genome-wide linkage and association studies, have largely focused on Neuroticism (Calboli *et al.*, 2010; Gillespie *et al.*, 2008; Hettema *et al.*, 2009; Kuo *et al.*, 2007; Shifman *et al.*, 2008; van den Oord *et al.*, 2008). A few studies have also included other traits, such as Extraversion (Gillespie *et al.*, 2008; Terracciano *et al.*, 2010b).

So far, only two GWASs of a personality trait and a meta-analysis of GWAS data have been published (de Moor *et al.*, 2011; Terracciano *et al.*, 2010b; Verweij *et al.*, 2010). Terracciano *et al.* (2010b) reported the first GWA results of about 4000 individuals for all five dimensions of personality, as measured by NEO-PI-R. The association of Neuroticism with SNAP25, Extraversion with BDNF and two cadherin genes (CDH13 and CDH23), Openness with CNTNAP2, Agreeableness with CLOCK, and Conscientiousness with DYRK1A was shown, but the effect sizes were small, and most of the associations failed to replicate in their follow-up samples. The back-to-back publication of the GWAS of Cloninger's temperament scales was reported (Verweij *et al.*, 2010). They identified no genetic variants that contributed significantly to personality variation.

Recently, only one meta-analysis of GWA data for personality was carried out in 10 discovery samples (17,375 adults) (de Moor *et al.*, 2011). Personality scores were based on the NEO-PI. The results showed genome-wide significance for Openness to Experience near the RASA1 gene on 5q14.3 and for Conscientiousness in the brain-expressed KATNAL2 gene on 18q21.1. However, in silico replication did not show a significant association of the top SNPs with personality scores.

Conclusions and Future Directions

With respect to the previously discussed association studies in the personality genetic study, there are several limitations. One of them is a lack of uniformity in modeling and measuring the personality phenotype. It is necessary to develop a uniform phenotype using major personality inventories and a large sample size. The abundant failures to replicate results of association studies suggest that the effects of candidate genes (SERT, DRD4, and so on) on personality traits must be small. Other as yet unknown genes may exert a greater

effect on the personality traits.

As mentioned above, there are no clear, replicable findings to date in GWASs on personality traits. In their studies, the environmental variables were not considered, and the age range of subjects was broad, which may be the reasons for the negative results. The twin studies consistently show that the environment explains about 50% of the variance. In the case of personality, the researchers should take the importance of the environment for the personality trait into account. The age range of subjects should be narrowed down, because its broad range might conceal a true association.

The other variants, including copy number variation and rare variants that are currently not captured in searching for common variants, may play a role in explaining variation in personality. In future work, next-generation sequencing may show more genetic variants that account for the heritability of complex traits, including personality. It is expected that knowledge of the biological mechanisms in normal personality can contribute to our understanding of personality disorder. On the other hand, by searching for "personality genes," we want to identify candidate genes for psychiatric disorders.

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