

# Genetics of the Human Personality

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## Abstract

Heritability of human personality traits is estimated in the range from 30% to 60%. A polygenic model which suggests interactions of multiple genes with each other and environment is recently preferred by researchers. One of the reasons why a psychiatrist should be aware of this issue is that personality traits of healthy persons may represent endophenotypes of psychopathology, and thus predict potential mental health problems.

The authors searched the PubMed database using key words “gene” and “novelty seeking”, “neuroticism”, “harm avoidance”, “self-transcendence”, “extraversion”, “impulsivity”, or “anti-social” in 2009.

This review covers genetic background of major human personality traits like novelty seeking, neuroticism, extraversion, impulsivity, or antisocial behavior. Results of recent meta-analyses with potential neurobiological mechanisms and possible transitions to Axis I mental disorders are presented. The authors also discuss possible confounding variables in genetic association studies into the human personality as a phenotype under study, assessment instruments, age, gender, epigenetic mechanisms, ethnic diversity, sample size, gene-gene, and gene-environment interactions.

A full understanding of genetic principles of the human personality and the role of social environment may be a fundamental step to an effective causal treatment and prevention of mental disorders in the future.

## INTRODUCTION

# H

uman personality is determined by a complex interaction of biogenetic and environmental variables. Normal personality traits have been repeatedly shown to be influenced by genetic factors with heritability estimates ranging from 30% to 60% (Savitz & Ramesar 2004). The non-shared environment accounts for the remaining 40% to 70% of the variance. Shared environmental factors are usually found to be of minor or no importance (Bouchard & Loehlin 2001; Ebstein et al 2002; Savitz & Ramesar 2004). A polygenic model recently seems to be the most promising one (Noblett & Coccaro 2005).

There are several reasons why psychiatric research should be focused on the role of genes in development of a human personality: Understanding of molecular base of normal personality is a logical prerequisite for research into neurobiology of an abnormal one, and comorbidity with Axis I mental disorders. Normal and abnormal personality have a common structure (Krueger 2005). Personality traits of healthy persons (e.g. aggressive-impulsive traits) are closer to the genetic effects than psychiatric syndromes, so that they may represent endophenotypes of psychopathology (e.g. suicidal behavior) (Baud 2005). The distinction between mental health and disease is rather quantitative than qualitative (Ritchie & Touchon 2000). Personality disorders may be in some cases related to susceptibility to major Axis I disorders (e.g. schizotypal personality disorder to schizophrenia, avoidant personality disorder to social phobia or generalized anxiety disorder) (Siever 2005; Herpertz et al 2007). Genes which in certain combinations can lead to mental disorders are genes for normal personality traits (Benjamin et al 2001).

The purpose of this paper is to review the current literature addressing genetic factors important for formation of a human personality to facilitate further research.

## METHODS

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he authors have repeatedly searched the PubMed database (<http://www.ncbi.nlm.nih.gov/sites/entrez>) using the key words “personality AND gene” during the year of 2009. The intent was to cover molecular aspects of a normal and abnormal human personality with possible transitions to mental disorders. To avoid an enormous number of references, recent summary works published in journals with a high impact factor and essentially meaningful recent original articles were preferred. The PubMed search was completed by using the key words “gene” and “novelty seeking”, “neuroticism”, “harm avoidance”, “self-transcendence”, “extraversion”, “affective instability/impulsivity”, or “antisocial” by the help of “Advanced Search” and “Meta-Analysis” functions on November 18th, 2009.

## RESULTS

### Novelty seeking

The beginning of molecular study of genes for normal personality dates back to 1996, when association of particular variants (long alleles; seven-repeat allele) of the highly polymorphic Dopamine D4 Receptor gene (DRD4; 11p) with the personality trait of novelty seeking (NS) was reported by two groups (Benjamin et al 1996; Ebstein et al 1996). The seven-repeat allele may result in a reduced response to dopamine leading to impaired inhibitory control.

The meta-analytical review of 20 studies (subjects N = 3 907) of the association between DRD4 polymorphism and novelty seeking by Ebstein et al. (2002) describes no association on average (average  $d = 0.06$  with 95% CI of  $\pm 0.09$ ), where 13 reports suggest that the presence of longer alleles is associated with higher novelty seeking score and seven reports suggest the opposite.

Rogers et al. (2004) investigated whether there is an association between a polymorphic 120 base pairs repeat in the 5'-untranslated region of the dopamine D4 receptor gene and NS. The authors genotyped four separate groups from psychiatric clinical studies. There were significant associations with NS in the groups of bipolar ( $p < 0.01$ ) and alcoholic ( $p < 0.01$ ) families containing 267 and 172 subjects, respectively. Subjects who were homozygous for the single-copy allele (ss genotype) had higher mean NS scores. This trend was also observed in the two other studies that contained unrelated subjects diagnosed with depression ( $N = 143$  and  $N = 148$ ). In the data combined from all four clinical groups, those genotyped as ss had higher mean scores for all four NS subscales with significant associations for impulsivity ( $p < 0.001$ ), extravagance ( $p < 0.05$ ), disorderliness ( $p < 0.05$ ), and total NS ( $p < 0.001$ ).

According to Lusher et al. (2001) who reviewed the recent research, it can be concluded that there may be an association with DRD4 long-repeat genotype and NS amongst severe drug-dependent (heroin, nicotine) populations.

Munafó et al. (2008) conducted a meta-analysis of published studies of the association between the DRD4 variable number of tandem repeats (VNTR; 36 samples) and C-521T (11 samples) polymorphisms and human approach-related personality traits (novelty seeking, extraversion, and impulsivity) in nonpsychiatric adult populations. The authors supplemented literary data with their own association study in a sample ( $N = 309$ ) with extreme extraversion scores selected from 40 090 individuals. The association of the C-521T polymorphism was only present for novelty seeking and impulsivity ( $p < 0.001$ ), and may account for up to 3% of phenotypic variance. The T allele is associated with a reduction in transcription levels of the D4 receptor of up to 40% compared with the C allele. The VNTR polymorphism was not associated with approach-related personality traits.

### Neuroticism

Neuroticism is an enduring tendency to experience negative emotional states like anxiety, anger, guilt or depression. Neuroticism is usually measured on the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck 1975) or the Revised NEO Personality Inventory (NEO-PI-R) (McCrae & Costa 1997). The first report by Lesch et al. (1996) suggested that genetically modulated activity of the serotonin transporter protein affects the development of anxiety-related traits.

Lesch (2001) subsequently reviewed published data on the association between the 5-HT transporter gene-linked polymorphic region (5HTTLPR; 17q) and anxiety-related traits in general populations and patient samples (studies  $N = 20$ ; subjects  $N = 4\,788$ ). The effect sizes for the 5-HTTLPR-personality associations indicate that this variable number tandem repeat (VNTR) polymorphism has a moderate influence of approximately 0.30 standard deviation units. This corresponds to 3-4% of the total variance. 5-HTT may affect personality traits via an influence on brain development and amygdala reactivity. Twin studies have consistently demonstrated that genetic factors contribute 40-60% of the variance in neuroticism. At least 10-15 genes are predicted to be involved. The contribution of the shared environment is very small, accounting for only 5% of the variance. The nonshared environment accounts for about 35% (Canli 2008).

Sen et al. (2004a) performed a meta-analysis of 26 studies investigating the association between a functional serotonin transporter promoter polymorphism 5-HTTLPR and anxiety-related personality traits. In the overall analysis ( $N = 5\,629$  subjects), they found suggestive evidence for an association between the 5-HTTLPR short allele and increased anxiety-related personality trait scores ( $p = 0.087$ ). When the analysis was stratified by inventory type, there was a significant association between 5-HTTLPR and NEO (the Neuroticism-Extraversion-Openness Inventory) neuroticism ( $p < 0.001$ ).

The short variant of the 5-HTTLPR polymorphism reduces the transcriptional efficiency of the 5-HTT gene promoter, resulting in decreased 5-HTT expression and 5-HT uptake. This seems to be inconsistent with the fact that anxiety may be treated with SSRI antidepressants, which also decrease serotonin re-uptake from the synapse by blocking the serotonin transporter. The explanation strongly supported by recent findings in rodents and nonhuman primates is that the 5-HTT may affect personality anxiety traits via an influence on brain development and plasticity (Lesch et al 2002).

Brain-derived neurotrophic factor (BDNF) is involved in cell survival, various neurotransmitter systems, hippocampal long-term potentiation, regulation of stress, and anxiety-related behaviors (Hemmings et al 2008). Five cross-sectional studies related to the BDNF gene (11p) Val66Met polymorphism and the Neuroticism scale of NEO-Personality Inventory with 1 633 subjects without psychiatric diagnoses were analysed by Frustaci et al. (2008). Both Met/Met and Val/Met individuals, as compared to Val/Val, showed a statistically significant lower neuroticism score (standardized mean differences -0.24 and -0.11, respectively).

Kendler et al. (2006) found that neuroticism strongly predicted the risk for major depression. The genetic correlation between neuroticism and major depression was 0.46 for women and 0.47 for men.

### Harm avoidance

In a study with 157 unrelated healthy Hungarian Caucasians, Szekely et al. (2004) observed a significant DRD4 (11p) × 5-HTTLPR (17q) interaction for harm avoidance. The subgroup with a ss 5-HTTLPR and seven-repeat DRD4 genotype showed a higher mean harm avoidance score than the other groups.

Minelli et al. (2009) in the association study on 195 healthy Italian Caucasian individuals reported on the T/G polymorphism at codon 928 in the Ionotropic Kainate Glutamate Receptor 3 gene (GRIK3; 1p) that causes a serine to alanine change at position 310 in the extracellular N terminus of the protein. The personality traits were measured by the self-rating Temperament and Character Inventory (TCI) scale. The Ala allele in homozygosity was associated with higher scores in harm avoidance ( $p < 0.05$ ), in addition to lower self-directedness ( $p < 0.001$ ) and cooperativeness ( $p < 0.005$ ) scores. This pattern of TCI scores is similar to that observed in depressed patients (Smith et al 2005).

### Self-transcendence

Two hundred male nonHispanic Caucasian subjects were administered the TCI and genotyped at the 48 base pair repeat polymorphism of the DRD4 gene (11p) by Comings et al. (2000) in California. The DRD4 gene was strongly associated with self-transcendence ( $p < 0.005$ ). The highest scores were in those carrying any  $>4$  repeat alleles. This may be a function of the high concentration of the dopamine D4 receptor in the cortical areas, especially the frontal cortex.

### Extraversion

Mitochondria is the major site of energy production in cells, therefore, mitochondrial abnormality may affect functions of brain which require high levels of energy consumption. Kato et al. (2004) investigated a role of two mitochondrial DNA polymorphisms in personality traits using the NEO PI-R scores in 238 healthy Japanese volunteers. Subjects with the 5178A genotype showed significantly higher extraversion score than those with the 5178C genotype ( $p < 0.05$ ).

Genetic factors that influence individual variation in extraversion and neuroticism appear to account entirely for the genetic liability to social phobia and agoraphobia. This was found by Bienvenu et al. (2007) in a study with 7 800 U.S. Caucasian twins. The results indicate the importance of both low extraversion and high neuroticism as personality endophenotypes for social phobia and agoraphobia.

### Affective instability/impulsivity

Based on a MedLine search of articles on rapid cycling in bipolar disorder, MacKinnon & Pies (2006) came to the conclusion that affective instability (rapid switching of mood) may be a highly productive endophenotype toward the understanding of disorders of mood regulation. The same genetic mechanisms affecting temporo-limbic regions may drive both the rapid mood switching in bipolar disorder and the affective instability of borderline personality disorder.

Impulsive aggression has been shown to be at least partially heritable, as established by both twin and adoption studies, with suggested heritability estimates ranging from 0.20 to 0.62 (New & Siever 2003). Abnormalities in central serotonergic activity have been consistently found to be associated with measures of impulsive aggression in patients with personality disorders. These findings will help to identify endophenotypes, which will make genetic studies in this complex area much more powerful. The endophenotype concept in psychiatry was comprehensively described by Gottesman & Gould (2003).

Around 45% of the variance in self-reported impulsivity is accounted for by nonadditive genetic factors (Congdon & Canli 2008). Dopamine D4 Receptor (DRD4; 11p), Dopamine Transporter (DAT; 5p), and Catechol-O-Methyltransferase (COMT; 22q) genes are the most promising candidates.

The study by Munafó et al. (2008) proving the association between the DRD4 gene C-521T polymorphism and impulsivity ( $p < 0.001$ ) has been mentioned in the paragraph "Novelty seeking".

### Antisocial behavior

Most twin and adoption studies found evidence for heritabilities of adult antisocial behavior between 0.40 and 0.60 (Jacobson 2005). Genetic factors appeared to be particularly important for the development of more severe, life-course persistent patterns of antisocial behavior. Individual adverse environmental experiences may trigger latent genetic liability to antisocial behavior.

Caspi et al. (2002) studied a large sample of male children from birth to adulthood to determine why some children who are maltreated grow up to develop antisocial behavior, whereas others do not. A functional polymorphism in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA; Xp) was found to moderate the effect of maltreatment. Maltreated children with a genotype conferring high levels of MAOA expression were less likely to develop antisocial problems. In a recent meta-analysis, the original finding of Caspi et al. was replicated (Kim-Cohen et al 2006).

The MAOA enzyme metabolizes neurotransmitters involved in stress regulation. The short MAOA gene variant may make children vulnerable to any maltreatment they experience. This sensitivity might spark anxiety, hyperactivity, impulsivity, or aggression. These mental and behavioral perturbations could set the stage for antisocial behavior (Arehart-Treichel 2006).

The interaction between MAOA and childhood maltreatment in the etiology of antisocial personality disorder appears to be one of the few replicated findings in the molecular genetics of personality disorders (Reichborn-Kjennerud 2008).

## DISCUSSION

Results of genetic association studies of the human personality may be influenced by following confounding variables:

### **R** Phenotypic characterization of personality traits

E.g. anxiety can be assessed as a presence of an anxiety disorder, or anxiety-related personality traits (neuroticism, harm avoidance) in healthy subjects. Depending on the definition of anxiety phenotype, the result of a genetic association study may be statistically significant or nonsignificant (Frustaci et al 2008).

### Instruments to measure personality

Self-report personality inventories which are recently used the most frequently include the Revised NEO Personality Inventory (NEO-PI-R) (McCrae & Costa 1997), Tridimensional Personality Questionnaire (TPQ) (Cloninger 1987), and Temperament and Character Inventory (TCI) (Cloninger et al 1993).

Munafó et al. (2005) gave an account of the influence of measurement instrument on results of genetic association studies on human personality. In a meta-analysis of 24 studies on the serotonin transporter gene and anxiety-related personality traits, they found a significant contrast between the S/S and L/L groups for TCI/TPQ harm avoidance studies ( $p=0.0024$ ) but not NEO neuroticism ( $p=0.9757$ ).

The self-judgement of the experimentee may not always correspond with the reality. Observer ratings were used only in a small number of studies (Eley et al 2003).

### Age

Cloninger et al. (1991) reported a negative correlation of age and novelty seeking based on a study of a U.S. sample of 1 019 adults. The age effects are consistent, continuous and found in different cultures. They are explaining at most 4% of the variance in TPQ (Tridimensional Personality Questionnaire) scores (Ebstein et al 2002). Krueger (2005) stated that “personality disorders tend to favor youth and rates of personality disorders may decline with age” based on epidemiological data from three studies.

### Gender

Fanous et al. (2002) investigated 863 male-male MZ (monozygotic), 649 male-male DZ (dizygotic), 506 female-female MZ, 345 female-female DZ, and 1 408 opposite-sex twin pairs, and concluded that “there may be sex-specific genes influencing neuroticism”.

In a meta-analysis of five independent studies on MAOA, maltreatment, and gene-environment interaction predicting children’s mental health, Kim-Cohen et al. (2006) demonstrated that the association between maltreatment and mental health problems is significantly stronger in the group of males. This is probably caused by processes involved in X-chromosome inactivation and MAOA gene expression in females.

### Epigenetic mechanisms

Epigenetic differences between monozygotic (MZ) twins may modulate differences in diverse phenotype, from personality to disease (Haque et al 2009). Neither environment nor differences in DNA sequence can fully account for phenotypic discordance among MZ twins. Epigenetic factors include skewed X-inactivation in female MZ twins, imprinting (differential expression of genes inherited from the mother or father), hypoacetylation of histone H4, and DNA methylation at CpG islands. DNA methylation, which modifies gene expressions and is potentially reversible, can be inherited across generations or occur de novo.

### Health or disease

If a depressed subject fills in a self-report personality inventory, the answers may be biased by self-depreciation and self-accusation. The answers of a subject with psychosis may likewise be disrupted by lack of insight and diminished contact with reality. That is why genetic research into the human personality should be rather performed in mentally healthy, or at least remitted individuals.

### Culture

Cultural variables modify or mask the effect of genetic polymorphisms. E.g. in a religious population of Southern Europe, suicidal activity in genetically predisposed people may be partially averted by devotional principles.

### Ethnic diversity

Because the frequency of alleles may vary across populations, ethnically stratified samples may produce spurious results (Savitz & Ramesar 2004). Family-based association studies like transmission disequilibrium test (TDT) (Spielman et al 1993) can be used to avoid ethnic stratification artifacts.

### Sample size

A putatively weak relationship between genotype and phenotype should only be detectable through the use of large sample sizes. Sample sizes of 350 or more are required to provide the necessary statistical power to adequately reject the null hypothesis (Savitz & Ramesar 2004).

### Gene-gene interactions

Benjamin et al. (2000) examined DRD4, 5-HTTLPR and COMT polymorphisms for association with TPQ personality factors in 455 Israeli subjects. Significant gene-gene interactions ( $p < 0.05$ ) were observed by multivariate and univariate ANOVA analyses. In the absence of the short 5-HTTLPR allele and in the presence of the high enzyme activity COMT Val/Val genotype, novelty seeking scores were higher in the presence of the DRD4 seven-repeat allele. Sen et al. (2004b) suggested a weak gene-gene interaction in NEO-PI neuroticism in 384 subjects. The effect of 5-HTTLPR might be dependent on the Pro385Ser variant of the GABA(A) Receptor alpha6 subunit gene (5q).

### Gene-environment interplay

Gene-environment interplay is a general term that covers several divergent concepts (Rutter et al 2006). Gene-environment correlations (rGE) concern genetic influences on people's exposure to particular sorts of environment. They may be active (genetic effects serve to select the environment, e.g. reading in a library versus playing with friends on the football field) or evocative (e.g. some children irritate their parents which act roughly in response). On the other hand, gene-environment interactions (GxE) reflect genetic variation in susceptibility to the environment. Kim-Cohen et al. (2006) studied 975 Caucasian boys in England and Wales. Monoamine oxidase A gene functional polymorphism in the promoter region (low vs high MAOA activity), physical abuse exposure, and children's mental health were assessed. Among children who were exposed to physical maltreatment, boys with the low-activity MAOA allele had mental health problem (antisocial behavior, attentional problems, emotional problems) scores that were half a standard deviation higher than boys with the high-activity allele.

In a prospective-longitudinal study of a representative cohort of 847 Caucasian New Zealanders born in the early 1970s, Caspi et al. (2003) tested why stressful experiences lead to depression in some people but not in others. A functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene was found to moderate the influence of stressful life events on depression. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele.

## CONCLUSIONS

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Complex human traits like personality involve multiple interacting genetic and environmental determinants. An attempt to link any given polymorphism to the operation of a single behavioral system may be a great oversimplification. The genetic basis of the human personality and its relation to prospective psychopathology will be discovered in the future using whole genome scans (WGS), microarray-based CpG island methylation measurement, detailed knowledge of life experience factors, and sophisticated statistical tools in sufficiently large and ethnically homogenous populations. Meta-analyses may help to detect true genetic effects by pooling data from several studies. Integration of genetic research in psychiatry with other experimental methods as brain imaging, electrophysiology or neuropsychology will likewise bring a more complex view.

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