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Modulation of a number of genes on personality traits in a sample of healthy subjects

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HIGHLIGHTS

- *ADRA2B*, *HTR2A* and *SHBG* may be involved in the modulation of personality in healthy subjects.
- Present findings confirmed previous reports on the influence of further genes in the modulation of personality.
- Exploring the role of new genes in personality modulation is needed to replicate and extend present results.

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ABSTRACT

A large number of studies investigated the genetic modulation of personality with mixed results. As a confirmatory analysis of previous findings, we firstly examined the association between several previously examined single nucleotide polymorphisms (SNPs) and personality traits in a sample of 158 healthy subjects. As a secondary aim, we tested the potential modulation of additional never previously investigated genes on personality. A blood sample was collected and the Temperament and Character Inventory (TCI) has been administered to all participants. Multivariate analysis of covariance, controlling for sex and age, was used to test SNP influence on TCI scores. Examination of previously studied gene variants showed an effect of adrenergic alpha 2B receptor (*ADRA2B*) on Cooperativeness and of serotonin receptor *HTR2A* on Self Directedness. Examination of new variants revealed that sex hormone binding protein (*SHBG*) was associated with reward dependence. Moreover, several additional variants showed a tendency towards association with some TCI traits, confirming previous results. This study suggests that *ADRA2B*, *HTR2A* and *SHBG* genes may be involved in the modulation of personality in healthy subjects. The major limitation of this study was the small sample size.

1. Introduction

Temperamental traits are stable representations of emotional, motor and attention reactivity to stimulation, as manifested by an organized pattern of behavioral responses across a range of contexts. These traits are biologically determined and essentially unchanged throughout adulthood [1–3]. The development of temperamental traits is a multifactorial process involving non-linear interactions of multiple genes and environmental factors [1–5]. Studies on population have shown that approximately 30–40% of the variability in personality is genetically determined [6–8].

Cloninger proposed seven personality dimensions [5,9,10]: four temperamental dimensions (novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (P)) and three character dimensions (self directedness (SD), cooperativeness (C) and self transcendence (ST)). The assumption that variability in these traits is linked to variability in underlying gene variants has

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generated a large number of studies [11–13]. Temperamental variation is thought to be influenced by neurotransmitter pathways. HA appears to be mainly influenced by serotonergic and dopaminergic systems [13–15]. C and ST were also found to be mainly associated with serotonergic system [1–3,5,16]. NS was found to be mainly influenced by dopamine, monoamine oxidase and catechol-O-methyl transferase (*COMT*) genes [4,5,17,18]. RD appears to be mostly influenced by both noradrenergic system [6–8,11,16,19] and *COMT* [5,9,10,20]. However, no clear neurotransmitter basis has been reported for P and SD [11–13,21].

Previous studies have also focused on new candidate genes, belonging to systems involved in CNS cell proliferation, development, transmission of nerve impulses and hormonal regulation [13–24].

Recently, the genetic modulation of personality has been investigated using genome-wide association studies (GWAS) [25], but with unsatisfactory results [25,26]. Only one large GWAS [27] revealed positive findings, however the associations were not replicated in independent samples. These negative results encourage new investigation of genetic polymorphisms in association with personality.

The primary purpose of this study was to explore the potential modulation of genetic polymorphisms previously investigated in literature (Table 1) on personality traits measured by the Temperament and Character Inventory (TCI) in a sample of healthy subjects. The secondary aim was to investigate for the first time the role of additional gene variants not previously reported in literature: *SHBG*, *TDO2*, *CCR5*, *FOS*, *HSP70*, *IL2*, *TSHB* and *AR* genes (Table 1). These last genes have been selected to investigate further systems that could influence personality, such as hormonal and inflammatory ones.

2. Materials and methods

2.1. Sample

A total of 158 unrelated healthy Caucasian volunteers was recruited among university students from Southern California as controls for a National Institute of Drug Abuse sponsored study of genetic factors in drug abuse/dependence [1–3,28]. Before the enrollment, an anamnestic schedule was filled in to assess the presence of any Axis I disorder, medical condition or pharmacological treatment and psychiatric familial history, all considered as exclusion criteria. Subjects were screened with the Michigan Alcoholism Screening Test and subjects with scores above the standard cut-off of 5.0 were excluded as well.

All participants were informed of the purpose of the project and the experimental procedures. Prior to study participation subjects signed a written informed consent. The study was approved by the Institutional Review Board at the Jerry L. Pettis Memorial Veterans Administration Medical Center, Loma Linda, California, and carried out in accordance to the ethical standards laid down in the 1964 Declaration of Helsinki. The present sample has been previously investigated [1–5,28,29].

Table 1
Investigated genes, their positions, biological functions and Hardy–Weinberg equilibrium (HWE). Data from snpper.chip.org or from omim.org. Haploview 4.2 was used to perform HWE test.

	Genes	Chromosome	Position	Function	HWE χ^2, p
ADRA2A	Adrenergic alpha 2A receptor	10	112,836,790–112,840,661	Coding protein	50.9, <0.001
ADRA2B	Adrenergic alpha 2B receptor	2	96,778,626–96,781,888	Coding protein	0.88, 0.35
ADRA2C	Adrenergic alpha 2C receptor	4	3,768,296–3,770,252	Coding protein	0.02, 0.90
COMT	Catechol-O-methyltransferase	22	19,929,263–19,957,497	Biosynthesis enzyme	0.03, 0.86
MAOA	Monoamine oxidase A	X	43,515,409–43,606,068	Catabolic enzyme	
Males					13.3, <0.001
Females					0.02, 0.88
DRD2	Dopamine receptor D2	11	113,280,318–113,346,001	Coding protein	0.02, 0.88
DRD3	Dopamine receptor D3	3	113,847,557–113,897,899	Coding protein	0.03, 0.86
DRD5	Dopamine receptor D5	4	9,783,258–9,785,633	Coding protein	13.6, <0.001
DBH	Dopamine beta-hydroxylase	9	136,501,485–136,524,468	Coding protein	0.85, 0.35
DAT1	Dopamine transporter 1	5	1,392,904– 1,445,542	Coding protein	7.14, <0.001
HTR1A	Serotonin receptor 1A	5	63,256,279–63,257,546	Coding protein	0.26, 0.61
HTR1B	Serotonin receptor 1B	6	78,171,948–78,173,120	Coding protein	0.26, 0.61
HTR1D	Serotonin receptor 1D	1	23,518,389–23,521,222	Coding protein	27.72, <0.001
HTR2A	Serotonin receptor 2A	13	47,407,513–47,471,169	Coding protein	0.61, 0.43
HTR2C	Serotonin receptor 2C	X	113,818,551–114,144,625	Coding protein	
Males					13.6, <0.001
Females					0.26, 0.61
5-HTTLPR	Serotonin transporter	17	28,523,375– 28,562,953	Coding protein	0.66, 0.41
TPH1	Tryptophan hydroxylase 1	11	18,042,084–18,062,335	Coding protein	21, <0.001
TDO2	Tryptophan 2,3-dioxygenase	4	156,824,847–156,841,551	Biosynthesis enzyme	3.04, 0.08
GAD1	Glutamate decarboxylase 1	2	171,673,200–171,699,269	Coding protein	0.13, 0.71
GAD 2	Glutamate decarboxylase 2	10	26,505,236–26,590,049	Coding protein	0.79, 0.37
NOS1	Nitric oxide synthase 1 (neuronal cell)	12	117,650,979–117,799,582	Coding protein	11.93, <0.001
NOS3	Nitric oxide synthase 3 (endothelial cell)	7	150,688,144–150,711,687	Coding protein	0.03, 0.85
CYP3A4	Cytochrome P450 3A4	4	187,112,673– 187,134,616	Coding protein	0.47, 0.49
CRH	Corticotropin releasing hormone	8	67,088,612–67,090,846	Coding protein	0.001, 0.97
CCR5	CCR5 chemokine (C-C motif) receptor 5	3	46,411,633–46,417,691	Coding protein	0.02, 0.87
FOS	FBJ murine osteosarcoma viral oncogene homolog	14	75,745,481–75,748,936	Coding protein	2.22, 0.14
HSP70	Heat shock 70 kDa protein 12A	6	31,783,290– 31,785,718	Coding protein	2.22, 0.14
IL2	Interleukin 2	4	123,372,630–123,377,650	Coding protein	2.60, 0.11
SHBG	Sex hormone binding globulin	17	7,517,382–7,536,701	Coding protein	2.41, 0.12
TSHB	Thyroid stimulating hormone beta	1	115,572,415–115,576,942	Coding protein	1.40, 0.23
AR	Androgen receptor	X	66,763,873– 66,950,460	Coding protein	
Males					12.3, <0.001
Females					2.22, 0.14