Effect of the serotonin transporter gene (5-HTT) on personality dimensions in individuals without psychopathology

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Introduction. The aim of the present study was to assess the association between the serotonin transporter gene and the Temperament and Character Inventory (TCI) personality dimensions in subjects without psychopathology.

Method. Fifty seven individuals without psychiatric symptoms were assessed with the SCL-90, and the TCI. In all subjects a peripheral blood sample was taken to determine their genotypes, after informed consent. Three groups were formed according to the 5-HTT genotype: SS, SL and LL, and the TCI results were compared.

Results. There was no association among the 5-HTT genotypes and any of the TCI subscales. There were also no statistical differences among any of the three groups divided by genotype only according to the TCI scores, as well as when compared with historical controls.

Conclusions. These results are consistent with other studies that have not found associations among the different measurements of personality and 5-HTT genotypes. Likewise, our data suggest that our sample can be useful as a source of controls for later studies. This is the first study assessing TCI dimensions and the 5-HTT gene in the Mexican population.

Key words:
Personality. Genetics. Temperament. Character. Serotonin. 5-HTT polymorphism.

Actas Esp Psiquiatr 2006;34(5):303-308

Efecto del gen del transportador de la serotonina (5-HTT) sobre las dimensiones de la personalidad en individuos sin psicopatología

Introducción. El presente estudio se realizó con el fin de estudiar el efecto de los genotipos moleculares del transportador de la serotonina (5-HTT) sobre las dimensiones de la personalidad basadas en el Inventario de Temperamento y Carácter (ITC) en personas sin presencia de psicopatología.

Métodos. Participaron 57 individuos sin sintomatología psiquiátrica evaluados mediante el SCL-90 y que respondieron además el ITC. A todos se les tomó una muestra de sangre periférica para la determinación de sus genotipos previo consentimiento informado. Se formaron tres grupos según el genotipo del 5-HTT: SS, SL y LL, y se compararon los resultados del ITC entre cada grupo.

Resultados. No se encontró relación entre los genotipos del 5-HTT y ninguna de las subescalas del ITC. Tampoco se pudieron demostrar diferencias entre ninguno de los tres grupos de acuerdo únicamente a las puntuaciones del ITC en comparación con ellos mismos, ni con un grupo de controles históricos publicados anteriormente.

Conclusiones. Los resultados son consistentes con otros estudios en los que no se han encontrado asociaciones entre las diferentes medidas de la personalidad y los genotipos del 5-HTT. Asimismo, los datos sugieren que la muestra que participó en el presente estudio puede utilizarse como una fuente de controles para estudios posteriores. Éste es el primer estudio de asociación entre la personalidad y el gen del 5-HTT que se hace en la población mexicana.

Palabras clave:
Personalidad. Genética. Temperamento. Carácter. Serotonina. Polimorfismo del 5-HTT.

INTRODUCTION

The concept of personality has been widely discussed in recent years. On the contrary to the classical definitions that define personality as a series of internal processes (both stable and temporal) to face the environment[1], dimensional personality models have presently taken on more interest given the diversity of highly generalizable structures and traits among individuals. Authors such as Eysenck[2] (1970), Tellegen[3] (1985), Cloninger[4] (1987), Watson and Clark[5] (1993), etc., have developed dimensional personality models based on different factors that also stress relatively stable and transitory traits.

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Between 1987 and 1994, Cloninger[4,6] proposed a psychobiological model with seven personality dimensions, four on temperament and three on character. This model is based on biogenetic evidence on the structure that modifies the individual's adaptive response to harm, avoidance, award and persistence (temperament) and is complemented with the description of three character dimensions, focused on conscious and social learning of the individual in his/her setting. Thus, Cloninger developed an instrument called Temperament and Character Inventory (TCI)[6] for the study of personality.

The need to study both the etiology and epidemiology of personality disorders (PD) has recently arisen due to at least three fundament aspects: *a)* PD are common and have been found in different cultures and sociocultural settings; *b)* PD seriously affect individuals who suffer them and are seriously disruptive in societies, families and communities and, y *c)* the presence of a PD generally affects the course of other concomitant psychiatric disorders[7].

However, given that it is difficult to establish the onset of PD and that they are long duration clinical conditions, it is difficult to study their true incidence. Thus, their main epidemiological evidence has been found in regards to the study of their prevalence[8]. Frequency of community prevalence of PD generally ranges from 0.1%[9] to 13.5%[10]. The large variability of these results is explained by the use of different diagnostic instruments[7].

In addition to indicating the onset of PD as a complicated result and focusing on their prevalence, their etiology must be evaluated. This has led to the need of investigators from multiple disciplines to assess the different factors that influence temperament and character. From the inheritance linked etiology perspective, focus has been placed on analyzing the different genes that may predispose to certain behaviors, cognitive processes, personality traits and even personality disorders.

One of the most important molecules in the study of normal and pathological behavior is serotonin (5-HT). In the human, non-human primate and other mammal brains, 5-HT neurotransmission intervenes in the regulation of emotional behavior, cognition, sensorial processing, motor activity and circadian rhythms such as feeding, sleep and reproduction. Such diversity of physiological functions is due to the fact that 5-HT directs the activity and interaction of other neurotransmission systems[11].

The site of serotonin transporter reuptake (5-HTT) plays an important role in the regulation of serotoninergic transmission in regions related with motor behavior, emotional experience and memory[12]. Furthermore, 5-HTT is the main action site of some antidepressive and anxiolytic drugs, such as fluoxetine, that inhibit serotonin reuptake. Given that 5-HTT is the main regulator of serotoninergic activity, it has been suggested that its genetic variability may predispose behavior (e.g., personality traits)[11].

The 5-HTT gene in humans is coded in chromosome 17q11.2. It is made up of 14 or 15 exons separated by approximately 35kb[13]. In humans, 5-HTT gene transcription activity is regulated by a polymorphic repetitive element or 5-HTT gene linked polymorphic region (5-HTTLPR) located on the site where the transcription begins. This polymorphism of the promoter of the 5-HTTLPR reuptake site is unique among human primates and apes. In humans, most of the alleles are composed by 14 or 16 repeated elements (short or long allele, respectively). In the caucasian race population, it is known that allelic frequency is 57% for the long allele (L) and 43% for the short allele (S), with a 5-HTTLPR genotype distribution of 32% L/L, 49% L/S and 19% S/S[12]. In Mexico, allelic frequency for 5-HTT is very similar to that found in the caucasian race14.

Homozygotic cells for the L variant (L/L) of 5-HTTLPR produce higher concentrations of mRNA than cells that contain one or two copies of the S form (L/S or S/S). Other studies have suggested that the S form is associated with a lower expression and function of 5-HTT[13]. Furthermore, the short form has been associated with an increase in brain metabolism of the anterior cortex, posterior cortex, amygdala, fusiform gyri, dorsolateral prefrontal cortex and superior temporal cortex, areas that are mostly associated to perception and memory of visual, emotional stimuli and award stimuli in anxiety disorders and depression[15,16].

From the behavior perspective, it has been associated to subjects carrying the S allele with a greater susceptibility to present affective disorders[17-19], personality with anxious traits[12,20,21], increase in fear conditioned response[22] and impulsive behavior[23].

Furthermore, differences have been found between carriers of different 5-HTTLPR alleles in some behavioral measurements and brain metabolism, and other authors have conducted studies to assess the genes involved in vulnerability to have different personality traits. In a study conducted by Cloninger et al.[24], the authors performed tests to find associations between quantitative trait loci (QTL) and the subscale of harm avoidance of the Tridimensional Personality Questionnaire (TPQ), a preliminary version of TCI, by means of a screening of the human genoma. A total of 758 siblings from 117 nuclear families of alcoholics participated. They found a locus that accounted for 38% of the variance and detected significant evidence of interactions between loci (epistasis), given that all the loci as a whole explained a greater variance for harm avoidance (54%-66%). These results have given rise to a reconsideration of studies on psychology and genetics of the personality. This is because they stress the importance of evaluating genetic-environmental interactions in the prevalence of certain temperament and character traits and the possible effects in different neuromodulation systems (pleiotropic) of certain genes and that they finally determine clinical presence on certain personality traits or dimensions.

Lesch et al.[12] were the first investigators who were dedicated to the study of the relationship between polymorphism in the serotonin reuptake site promoter (5-HTTLPR) and personality. The authors conducted a study in which they found that individuals with allele S obtained higher scores on the neuroticism, anxiety and harm avoidance subscales than homozygotic individuals for the L allele (n = 505), measured with two personality instruments, TCI and Eysenck. This association was found both in population samples and in siblings (they were predominantly caucasians). Equally, in a study conducted by Greenberg et al.[21], similar results were found in a sample of 397 siblings, mainly female (84%). However, other studies that have also replied to the Lesch et al.[12] study have not found any association between possible 5-HTTLPR genotypes and personality traits, regardless of the sample size or race of the subjects evaluated[25-29].

As can be seen, there is controversy between the association of the 5-HTT gene and personality measurements. The differences reported in the literature may be due to different factors such as race, sample size and even the instruments used to measure personality. The present study was done in order to evaluate if there were differences between individuals according to polymorphic variants of the serotonin reuptake site (5-HTTLPR) between the scores of the different personality dimensions evaluated in the Cloninger Temperament and Character Inventory (TCI)6 in Mexican individuals without psychopathology.

METHODOLOGY

Participants

A total of 57 individuals with a mean age of 45 years participated in the study. They came by invitation to participate in the present study on genetics and personality in the PET-Cyclotron Unit of the Medical School of the National Regional University of Mexico. A total of 56% of all the participants were women.

All those individuals who had a score greater than two in the subscales cluster of psychiatric screening on the Symptom Checklist (SCL-90)[30,31] were excluded from the sample.

The individuals were assigned to one of three groups according to their 5-HTT genotype, so that 21 groups were included in the group of the S/S alleles, 21 in the S/L group and 15 in the L/L group. In addition, there was a historic control group of 54 participants previously evaluated by our same group in order to compare the TCI results[32].

Written informed consent was obtained from all the volunteers participating in the study, both for the evaluations and obtaining of genomic DNA. The project and informed consent were approved by the Ethics Committee of the different participating institutions.

Instruments

Temperament and Character Inventory (TCI)

The Temperament and Character Inventory[6] is a self-applicable instrument that is made up of 240 items that evaluate dimensionally the adaptive response of the individual towards novelty seeking, harm avoidance, award dependence and persistence as temperament factors and self-directedness, cooperativeness and self-transcendence as the 3 character dimensions. The test statements have two response options (true and false) for the participant to decide which is the one that best describes him/her.

The TCI has acceptable levels of validity and reliability for its use in the general and clinical population. The Spanish version of the instrument has a psychometric behavior similar to the original version[33].

Symptoms checklist (SCL-90)

The SCL-90[30,31] is a self-applicable screening test that evaluates presence of symptoms associated to psychiatric diseases. This variable was considered as an exclusion criterion in the present study. The instrument has a list of 90 items related with symptoms of 9 different psychopathologies (somatization, obsessive-compulsive, sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and general score). The responses of the participants receive different scores according to the option that best describes how much the statement mentioned bothered him/her during the last week, using a Likert type scale with five response options (0: never; 1: very few times; 2: sometimes; 3: many times; 4: always).

This scale has an elevated sensitivity to detect psychopathology in the general population, although its specificity is low[31].

Procedure

The participants were invited to collaborate in the present study in the PET-Cyclotron Unit of the Medical School of the UNAM. All the individuals voluntarily signed an informed consent letter when they accepted to collaborate in the investigation.

The participants were interviewed to obtain sociodemographic data and a brief clinical history was made. TCI and SCL-90 instruments were given individually for them to respond to. Additionally, peripheral blood was drawn from the forearm vein for subsequent molecular analysis.

The genomic DNA was obtained from the blood sample through the standard procedure[34]. Polymerase chain reaction (PCR) was done for the 5-HTTLPR polymorphism in a

total volume of 15 µl. It contained 1.8 mM of $MgCl^2$, 200 mM of dATP, 200 mM of dCTP, 200 mM of dTTP, 100 mM of dGTP, 100 mM of 7-deasa-dGTP, 0.96 units of AmpliTaq Gold polymerase (AmpliTaq Gold; Perkin Elmer, Norwalk, CT, USA), 1.3 µM primers (5'GGC GTT GCC GCT CTG AAT TGC and 5'GAG GGA CTG AGC TGG ACA ACC CAC) and 150 ng of genomic DNA. After the initial step of 10 minutes of denaturalization at 95 ºC, 45 cycles of 30 s were done at 30 s at 95 ºC, 30 s at 61 ºC and 1 min at 72 ºC, followed by a final step of 7 min at 72 ºC. The PCR products were separated in 2 % of highly melted agarose gel and then seen through ultraviolet light after ethidium bromide staining.

Table 1 Sociodemographic data

Group	SS	SL	LL	Controls	*p*
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	49.6 (14.9)	45.1 (16)	41.7 (16.8)	35 (8)	NS
Gender (women/%)	14 (67)	11 (52)	7 (47)	31 (57)	0.046*

RESULTS

The results of the study were analyzed comparing the mean scores of the different TCI dimensions among the S/S, S/L, L/L and control groups with a multivariate variance analysis (MANOVA), using the statistical program of S-Plus v. 2000®.

Table 1 shows the sociodemographic data of the participants, describing the means and standard deviations of age and gender according to each group.

As can be seen in table 1, there are no significant differences between the groups in age. However, in regards to gender, women have a consistently greater place among the groups analyzed (57 % in all). The significance in the gender percentage is due to the fact that the percentage of women is much greater than that of men in the S/S group and a little lower in the L/L group.

Table 2 shows the means and standard deviations of the TCI scores in the columns for each group analyzed and the MANOVA results. In the rows, each one of the TCI dimensions is given, abbreviated in English. The temperament factors are NS: novelty seeking; HA: harm avoidance; RD: reward dependence, and PE: persistence, while the character dimensions are SD: self-directedness; CO: cooperativeness and ST: self-transcendence.

Table 2 shows that there are no significant differences between any of the four groups for any of the TCI dimensions ($p > 0.05$). It can be stated that, in addition to the fact that the genotypal groups do not show any differences, they also show none when compared with the historic control group.

CONCLUSIONS

The present study was conducted in order to analyze the association between alleles of the gene linked polymorphic region of the serotonin transporter (5-HTTLPR) and the dimensions of the Temperament and Character Inventory personality dimensions[6,33] in individuals without psychiatric disease.

It is possible that no statistically significant differences were found between the TCI subscales and the 5-HTT poly-

Table 2 Mean of the TCI dimensions between the groups analyzed and MANOVA

Group	SS		SL		LL		Controls		F	*p*
TCI	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
NS	16.3	6.1	19.3	5.0	17.0	4.5	19.6	5.6	1.306	0.282
HA	13.6	5.6	12.7	5.6	13.3	5.0	13.6	6.3	0.102	0.959
RD	14.8	3.3	14.1	4.1	14.6	3.8	15.0	4.0	0.138	0.937
PE	4.4	1.7	4.9	1.4	5.4	1.9	5.3	1.7	1.177	0.371
SD	33.7	6.4	35.6	6.5	32.3	7.8	34.0	6.1	0.729	0.539
CO	32.7	5.7	32.8	5.0	32.2	5.4	31.9	5.9	0.053	0.984
ST	18.9	6.7	17.9	6.1	17.3	7.1	13.9	6.3	0.579	0.631

NS: novelty seeking; HA: harm avoidance; RD: reward dependence; PE: persistence; SD: self-directedness; CO: cooperativeness; ST: self-transcendence.

morphism variants because the sample was small and the standard deviations of the scores were very high regarding the measurements obtained. In addition, the fact that no differences were found between TCI, 5-HTT polymorphism genotype, and historic controls makes it possible to consider the participants of the present study as strong controls for subsequent investigations.

Some studies on the association of 5-HTTLPR and personality have already suggested that the influence of the gene on behavior predisposition is modest (approximately from 3% to 4% of the total and 7% to 9% of the genetic variance), while the genetic factors contribute from 40% to 60% of the variance for neuroticism and related traits, concluding that the influence of a single polymorphism on traits that are distributed normally is small among humans[35]. Our data coincide with those of these authors and give rise to the need to study other genes involved in the vulnerability of presenting different personality traits.

The fact that no statistically significant differences were found between the TCI subscales and the 5-HTT polymorphism variants is consistent with other studies in which this association has not been found[25-29]; even though, in turn, the results differ from those of other authors who have described a strong association between allele S and neuroticism, anxiety and harm avoidance scores[12,21]. However, lack of significance in the present study is explained by a lower N than that reported in the studies with the association.

However, as mentioned by Reiff and Lesch[36], the interpretation of the association studies between 5-HTTLPR and personality is controversial due to the constant use of non-representative samples, to the lack of studies in families, to the differences in the multiple measurements of personality applied, to the ethnic differences, etc. This necessarily leads to a careful interpretation of the findings in this material.

In summary, our results suggest the need to study other genes involved in the vulnerability of presenting different personality traits, of extending the samples of the participants to be evaluated, controlling the ethnic factors and measurement instruments of the traits to be studied. However, the relevance of the present study is found in the force of the participants as control individuals for future investigations on genetics and personality in addition to being the first report of a study of this type in the Mexican population.

REFERENCES

1. Allport GW. Personality: a psychological interpretation. New York: Holt, 1937.
2. Eysenck H. The structure of human personality. London: Methen, 1970.
3. Tellegen A. Structures of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In: Tuna AH, Maser JD, editores. Anxiety and the anxiety disorders. Hillsdale: Erlbaum, 1985; p. 681-706.
4. Cloninger CR. A systematic method for clinical description and classification of personality variants. Arch Gen Psychiatry 1987;50:975-90.
5. Watson D, Clark LA. Behavioral dosinhibition versus constraint: a dispositional perspective. In: Wegner y Pennebaker DM, editor. Handbook of mental control. New York: Prentice Hall, 1993; p. 506-27.
6. Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD. The Temperament and Character Inventory (TCI): a guide to its development and use. St. Louis, MO: Center for Psychobiology of Personality. Washington University, 1994.
7. Páez F, Rodríguez R, Pérez V, Colmenares E, Coello F, Apiquián R, et al. Prevalencia comunitaria de los trastornos de la personalidad. Resultados de un estudio piloto. Salud Mental 1997;20 (Suppl. 3):19-23.
8. De Girolamo G, Reich JH. Personality Disorders. Ginebra: World Health Association, 1993.
9. Leighton AH. My name is Legion: The Stirling County Study of Psychiatric Disorder and Sociocultural Environment. New York: Basic Books, 1959.
10. Zimmerman A, Coryell WH. Diagnosis personality disorders in the community: a comparison of self-report and interview measures. Arch Gen Psychiatry 1990;47:527-31.
11. Lesch KP, Mossner R. Genetically driven variation in serotonin uptake: is there a link to affective spectrum, neurodevelopmental, and neurodegenerative disorders? Biol Psychiatry 1998;44: 179-92.
12. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al. Association of anxiety related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996; 274:1527-31.
13. Lesch KP, Greenberg BD, Higley JD, Bennett A, Murphy DL. Serotonin transporter, personality, and behavior. Toward a dissection of gene-gene and gene-environment interaction. In: Benjamin J, Ebstein RP, Belmaker RH, editors. Molecular genetics and the human personality. Washington: American Psychiatric Publishing, 2002.
14. Nicolini, H. Genética de las conductas compulsivas. En: de la Fuente R, editor. Aportaciones recientes de la biología a la psiquiatría. México: Colegio Nacional, 2003.
15. Graff-Guerrero A, Alexanderson-Rosas E, Altamirano-Ley J, Estrada-Sánchez G, Gómez-Martín D, Méndez JC, et al. Diferencias en el metabolismo en estructuras límbicas de acuerdo de la variación alélica del polimorfismo 5HTTLPR del gen del transportador de serotonina: un estudio piloto con PET. Salud Mental 2004;27:11-21.
16. Graff-Guerero A, de la Fuente-Sandoval C, Camarena B, Gómez-Martín D, Apiquián R, Fresán A, et al. Frontal and limbic metabolic differences in subjects selected according to genetic variation of the SLC6A4 gene polymorphism. Neuroimage (in press).
17. Collier DA, Stober G, Li T, Heils A, Catalano M, Di Bella D, et al. A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. Mol Psychiatry 1996;1:453-60.
18. Ogilvie AD, Battersby S, Bubb VJ, Fink G, Harmar AJ, Goodwim GM, et al. Polymorphism in serotonin transporter gene associa-

ted with susceptibility to major depression. Lancet 1996;347: 731-3.
19. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-9.
20. Mazzanti CM, Lappalainen J, Long JC, Bengel D, Naukkarinen H, Eggert M, et al. Role of the serotonin transporter promoter polymorphism in anxiety-related traits. Arch Gen Psychiatry 1998;55:936-40.
21. Greenberg BD, Li Q, Lucas FR, Hu S, Sirota LA, Benjamin J, et al. Association between the serotonin transporter promoter polymorphism and personality traits in a primarily female population sample. Am J Med Genet 2000;96:202-16.
22. Garpenstrand H, Annas P, Ekblom J, Oreland L, Fredrikson M. Human fear conditioning is related to dopaminergic and serotonergic biological markers. Behav Neurosci 2001;115:358-64.
23. Camarena B, Ruvinskis E, Santiago H, Montiel F, Cruz C, González-Barranco J, et al. Serotonin transporter gene and obese females with impulsivity. Mol Psychiatry 2000;7:829-30.
24. Cloninger CR, van Eerdewegh P, Goate A, Edemberg HJ, Blangero J, Hesselbrock V, et al. Anxiety proneness linked to epistatic loci in genome scan of human personality traits. Am J Med Genet (Neuropsychiatric Genetics) 1998;81:313-7.
25. Ball D, Hill L, Freeman B, Eley TC, Strelau J, Riemann R, et al. The serotonin transporter gene and peer-related neuroticism. Neuroreport 1997;8:1301-4.
26. Ebstein RP, Gritsenko I, Nemanov L, Frisch A, Osher Y, Belmaker RH. No association between the serotonin transporter gene regulatory region polymorphism and the Tridimensional Personality Questionnaire (TPQ) temperament of harm avoidance. Mol Psychiatry 1997;2:224-6.
27. Flory JD, Manuck SB, Ferrell RE, Dent KM, Peters DG, Muldoon MF. Neuroticism is not associated with the serotonin transponder (5-HTTLPR) polymorphism. Mol Psychiatry 1999;4:93-6.
28. Jorm AF, Henderson AS, Jacomb PA, Christensen H, Korten AE, Rodgers B, et al. An association study of a functional polymorphism of the serotonin transporter gene with personality and psychiatric symptoms. Mol Psychiatry 1998;3:449-51.
29. Nakamura T, Muramatsu T, Ono Y, Matsushita S, Higuchi S, Mizushima H, et al. Serotonin transporter gene regulatory region polymorphism and anxiety-related traits in the Japanese. Am J Med Genet 1997;74:544-5.
30. Derogatis LR. Symptom Checklist-90-R: administration, scoring, and procedures manual. Minneapolis: National Computer Systems, 1994.
31. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale-preliminary report. Psychopharmacol Bull 1973;9:13-28.
32. Cruz-Fuentes C, Blas C, González L, Camarena B, Nicolini H. Severity of obsessive-compulsive symptoms is related to self-directedness character trait in obsessive-compulsive disorder. CNS Spectr 2004;9:607-12.
33. Sánchez de Carmona M, Páez F, López J, Nicolini H. Traducción y confiabilidad del Inventario de Temperamento y Carácter (ITC). Salud Mental 1996;19:5-9.
34. Lahiri D, Nurnberger JI Jr. A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. Nucleic Acids Res 1991;19:5444.
35. Plomin R, Owen MJ, McGuffin P. The genetic basis of complex human behaviors. Science 1994;264:1733-9.
36. Reiff A, Lesch KP. Toward a molecular architecture of personality. Behav Brain Res 2003;139:1-20.