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The role of genetics in the personality and its disorders: a clinical point of view

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The most important bibliography on the role of genetics in personality and its disorders has been reviewed from a clinical point of view. Following the introduction, the most relevant findings on genetics and the personality dimensions are compiled, focusing on Cloninger's Psychobiological Model. Regarding personality disorder, studies have been found on cluster A, mainly related to the schizotypal personality disorder, and on cluster B, mainly related to antisocial personality and borderline disorders. The bibliography on cluster C PD was limited. The review concludes with a discussion that stresses the possible usefulness of personality dimensions, considered as interphenotypes regarding both diagnostic aspects and treatment.

Key words:
Genetics. Personality. Personality disorders. Diagnose. Treatment.

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El papel de la genética en la personalidad y sus trastornos desde una perspectiva clínica

Desde un punto de vista clínico se ha revisado la bibliografía más destacable sobre el papel de la genética en la personalidad y sus trastornos. Tras la introducción se recopilan los hallazgos más relevantes sobre genética y dimensiones de personalidad, haciendo hincapié en el modelo psicobiológico de Cloninger. Respecto a los trastornos de la personalidad se han encontrado estudios sobre el clúster A, especialmente sobre el trastorno esquizotípico de la personalidad, y sobre el B, especialmente en relación con los trastornos antisocial de la personalidad y límite, siendo escasa la literatura sobre los trastornos del clúster C. La revisión finaliza con una discusión en la que se enfatiza en la posible utilidad de las dimensiones de personalidad, consideradas como interfenotipos, tanto en relación con aspectos diagnósticos como de tratamiento.

Palabras clave:
Genética. Personalidad. Trastornos de la personalidad. Diagnóstico. Tratamiento.

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INTRODUCTION

Importance and limitations

No conclusions can be drawn regarding the role of genetics and environment in Personality Disorders (PD) based on a single study or type of study. These can only be obtained through evidence based on a large number of investigations using very varied methodologies[1]. The frequent reviews on genetics of mental disease, specifically PD, are justified because one single article or small group of them can lead us to erroneous conclusions and/or those having little scientific consistency. One aspect that makes research on the genetics of mental disease more complex is the diagnostic difficulties[1]. If the different studies use different diagnostic criteria and even nosological ones, the task of integrating knowledge that these supply will unlikely increase the consistency of the conclusions that are being looked for.

This review aims to generate an evidence-based opinion from the articles reviewed regarding what directions should be established for the future beginning with the current classifications on personality and its disorders. Controversial aspects such as categorical-dimensional diathesis of the personality and its disorders, possibility of including direct cerebral measurements or the presence of some genetic markers (or biological ones of any type) in the psychiatric classifications should be considered. Specifically, the classifications of the personality disorders entail an added difficulty since there are no signs or symptoms but rather exaggerated or disadaptative personality traits.

Types of genetic studies in psychiatry

Initially, the importance of the logical chronology of the studies on genetic psychiatry should be clarified. Thus, in order to justify the study using molecular genetic techniques, it must first be demonstrated using epidemiological data that the genes may play a substantial etiological role[1]. These data are obtained from mainly three types of epidemiological genetic studies: family, twins and adoption. If these studies do not suggest that a disorder is inheritable, it is better to investigate the environmental causes and to not conduct molecular studies.

The family studies are the most frequent and important. They help to respond to the following initial question: is the disorder found more frequently in certain families? The study of twins helps to elucidate if the disease is caused by genes, the environment or both. And the studies on adoption aim to attribute the family transmission to the genes or to the psychosocial setting usually by comparison with some of the previously types.

THE CLONINGER PERSONALITY MODEL

Cloninger designed his general personality model in two stages: in the initial stage, he developed and evaluated a temperament model with three dimensions: novelty seeking (NS), harm avoidance (HA), and reward dependence (RD). It was hypothesized that they would correspond directly with the underlying genetic structure of the personality[2]. The Tridimensional Personality Questionnaire (TPQ) was designed to measure these dimensions[2]. The studies conducted with this instrument confirmed the temperament structure suggested by Cloninger, with the exception of the obtaining of a new dimension, the fourth one, that was called persistence (P).

The Cloninger model was subsequently modified to overcome some limitations. It was detected that the studies conducted with the TPQ had not taken the role of character and social learning into account. Another limitation was that the temperament dimensions distinguished personality subtypes but did not differentiate individuals with personality disorders or the social adaptation difficulties in individuals with extreme scores on the dimension but without adaptation problems.

Thus, the model was changed by adding three character dimensions to the personality component: self-direction (A), cooperativeness (C), and self-transcendence (ST)[3]. In this way, the Temperament and Character Inventory (TCI) maintained a strong theoretical and empirical support of the previously developed psychobiological models (including those of Eysenck, Gray and Zuckerman), while it overcame some of the limitations it had for clinical use since it included 24 subscales of the inferior order that offered clinically relevant information and seemed to be a good indicator of the presence of personality disorders according to the DSM-III-R[4].

The Cloninger model is a good starting point for research in genetics of the personality since three of its dimensions would be influenced by some neurotransmitters: the NS due to the genetic variability in the dopaminergic systems, the HA due to serotoninergics and the RD due to noradrenergics. Using this as a basis, the polymorphisms of the genes that code for receptors and transporters of the neurotransmitter molecules have been studied (table 1).

PERSONALITY DISORDERS

Cluster A

Cluster A of the diagnostic and statistical manual of mental disorders, DSM-IV-TR, includes the paranoid personality disorder (PPD), schizoid personality disorder (SPD) and schizotypal personality disorder (STPD)[29], the STPD being the nucleus where most of the genetic research is focused (table 2).

The genetic relationship between STPD and schizophrenia has been the object of many studies. The principal genetic-epidemiological design to analyze the possible relationship between both diseases consists in estimating the STPD in families of schizophrenia subjects. The results of the research suggest that the environment has an influence on the distribution of the diagnoses in at risk families although this influence is more likely to be produced in paranoid and personality borderline disorders than in STPD[38]. Considering STPD as a form of moderate phenotype of schizophrenia allows for a second analytic method that consists in analyzing the proportion of family members who have a severe phenotype of the disease (chronic schizophrenia) among the family members of subjects with a more moderate phenotype (STPD)[42].

In order to establish if STPD focuses more on families who have a greater risk of suffering schizophrenia it must be determined if STPD is transmitted through the family by itself and to what degree this transmission is due to genetic factors. To elucidate this point, the third type of analysis of heritability is used. This includes family, twin and adoption studies. As Battaglia and Torgensen indicate, up to 1996 two historical family studies had been done on STPD transmission, one family study, one study on adoptions and two studies on twins[41].

Having analyzed all the information, it can be deduced that the transmission of STPD is familial and that the genetic factors play a significant role, although there is the possibility that only part, and not all, of the disorder is transmitted. Including STPD in the spectrum of schizophrenia may increase the potency of the genetic analyses and provide clues in order to understand the nature and modes of its transmission[41]. At the same time, different authors consider that there are no robust familial studies on STPD that evaluate markers of phenotypal vulnerability, relative risk or heritability of these traits. That is why it is possible that STPD is genetically identical to some form of schizophrenia

Table 1 Genetics and Cloninger personality model

Authors	Resuts	F/A
Heath AC, 1994[5] Koopmans JR, 1995[6]	It is suggested that genetic factors would account for approximately 50% of the NS variance	F
Benjamin J, 1996[7] Ebstein RP, 1996[8] Ono Y, 1997[9] Kuhn KU, 1999[10] Noble EP, 1998[11] Strobel A, 1999[12] Tomitaka M, 1999[13]	A significant association between the dimension of NS and the DRD4 gene 7 repeat allele is observed	F
Jönsson EG, 1997[14] Bau CH, 1999[15] Gelernter J, 1997[16] Pogue-Geile M, 1998[17] Sander T, 1997[18] Sullivan PF, 1998[19] Vandenbergh DJ, 1997[20]	No significant association is observed between the NS and the DRD4 gene 7 repeat allele	A
Kluger AN, 2002[21]	No statistically significant association between the polymorphism analyzed in the DRD4 gene and NS dimension in the meta-analysis on 20 studies	A
Okuyama Y, 2000[22]	A significant relationship was observed between the NS dimension and a polymorphism in the promoter region of the DRD4 gene	F
Ekelund J, 1999[23]	An association between the 2 and 5 repeat alleles of DRD4 and high scores in NS is identified	F
Noble EP, 1998[24]	An interaction between the DRD4 and DRD2 polymorphisms is found since the NS dimension is more stressed when the three minor alleles of DRD2 and the DRD4 gene 7 repeat allele present together	F
Kuhn KU, 1999[10] Ebstein RP, 1997[25]	A gene-gene interaction between a polymorphism of the DRD4 receptor and the polymorphism Cys23Ser of 5-HT2C was found. When these polymorphisms were found in the same individual, they accounted for 13% of the RD variance and 30% of the P variance	F
Lesch KP, 1996[26]	The 5HTTLPR genotype was significantly associated with the HA dimension, more specifically with the subscales of concern and pessimism, fear of the unknown and fatigability	F
Cloninger CR, 1998[27]	A significant association was detected between HA and a locus on the chromosome 8p21-23, accounting for 38% of the trait variance. However, this result was obtained from relatives of alcoholics, so that its transference to healthy subjects is not clear	F
Kusumi I, 2002[28]	No direct relationship was found between personality traits measured with the TCI and 5-HT2A receptor function or the genetic polymorphism of the 5-HT2A gene receptor	A

F: is in favor of the genetic association; A: against the genetic association.

but with a weaker phenotype because of a combination of reduced penetrance, greater number of protective factors or lack of non-genetic factors, as viral or toxic agents. What does seem to be possible is that only one subgroup of STPD subjects would be genetically identical or would be related with the different forms of schizophrenia and the genetic vulnerability together with the corresponding markers could help to define this subgroup with clarify[47].

On a different level than that mentioned up to now, a series of specific neuropsychological indicators related with schizophrenia, and that has more recently been analyzed for the STPD, have been studied over the years. These indicators may be of great utility as phenotypal indicators in genetic linkage analyses[48] and according to these, there would be three endophenotypes that can be useful to understand the genetic responsibility in the STPD47. The neuropsychological indicators are

Table 2 Epidemiological genetics and cluster A personality disorders

Authors	Results	F/A
Torgensen S, 1984[30] Battaglia M, 1999[31]	28% monozygotic co-twins of subjects with STPD also have the disorder vs. 3% of dizygotic co-twins	F
Kendler KS, 1991[32]	The existence of two dimensions of STPD on which the genetic factors exert their influence in different grade is suggested	F
Kety SS, 1968[33]	Schizophrenia and its related disorders had a 20% incidence in biological relatives of subject with said disease while in the relatives of adopted subjects and controls, it was 6%	F
Kendler KS, 1994[34]	The previous study data were analyzed with the DSM-III criteria of schizophrenia and STPD exclusively, the respective frequencies being 12% and 3%. This becomes a frequency percentage of 21% and 5% when only the first degree family was considered	F
Kendler KS, 1993[35]	The rates of STPD and PPD are significantly greater among relatives of subjects with schizophrenia than among those of control subjects	F
Squires-Wheeler E, 1988[36] Squires-Wheeler E, 1989[37]	Small frequencies of STPD that are similar in family of subjects with schizophrenia and in those of subjects with mood state disorder are detected	F
Kringlen E, 1989[38]	In a small sample of the descendents of monozygotic twin pairs discordant for schizophrenia, no statistical significance was found in the spectrum of disorders related with schizophrenia in comparison with the descendents of healthy twins	A
Onstad S, 1991[39] Torgersen S, 1993[40]	A specificity in the familial transmission was observed because the incidence of STPD and/or PPD is significantly greater in the family members of subjects with schizophrenia than in those of subjects with mood state disorders	F
Battaglia M, 1996[41]	Familial risk of suffering schizophrenia from 0% to 8.4% according to the review of 12 subjects. Lower familial risk of suffering schizophrenia in subjects with STPD than in those with schizophrenia, suggesting polygenic model of the schizophrenia	F
Battaglia M, 1991[42] Siever LJ, 1990[43] Thaker G, 1993[44]	Greater risk of suffering schizophrenia, schizophrenia plus some cluster A PD or schizophrenia with functional psychosis in family members of subjects with STPD than in those of control subjects	F
Baron M, 1985[45]	Familial risk of STPD of 14.8%	F
Siever LJ, 1990[43]	Familial risk of STPD of 14.4%	F
Battaglia M, 1995[46]	Familial risk of STPD of 18.9%. Greater significant familial risk of STPD than PPD	F

F: is in favor of the genetic association; A: against the genetic association.

prepuse inhibition, supression of P50 evoked potential and anti-saccade paradigm.

Prepulse inhibition (PPI)

The repeated presentation of weak stimuli prior to a strong stimulus reduces the magnitude of the blinking reflex. Schizophrenic patients show a response having less inhibition than the normal subjects. Even clinical non-affected family members of schizophrenic subjects show a similar deficit49. Patients with STPD also have this deficit in comparison with normal subjects[50]. No definitive analysis of the inheritance pattern of PPI has been made in twins, but the modulation of this response using affective stimuli seems to be, at least partially, under genetic control since monozygotic twins (but not dizygotic ones) show similar changes in the amplitude of this response[51].

Suppression of P50 evoked potential

Multiple studies have found that there is a normal suppression of the second P50 potential, possibly due to the

activation of the inhibitory process of the first P5047. In normal individuals, the second P50 shows a decrease of 80%, it being detected from the end of adolescence until 65 years of age[52]. Schizophrenia patients[53], first degree family members[54] and subjects with STPD[55] show a reduced suppression of P50 in comparison with normal subjects.

Antisaccade paradigm

Control of the saccade (rapid eye movements which redirect gaze to a specific place) is a good measurement to differentiate subjects with schizophrenia from healthy subjects[47]. The non-psychotic first degree family members of subjects with schizophrenia and STPD generate a larger proportion of errors on this test[56]. In fact, 75% of the schizophrenic patients and 25%-50% of the relatives generate more errors than the worse one executed by the control subjects[57].

The inhibitory deficits in the information processing in individuals with STPD who are not taking medication and in relatives of clinically unaffected subjects with schizophrenia suggest that these neurobiological traits do not depend on the condition nor are secondary to factors such as effects of the medication or generalized psychosis, disorganization or underlying cerebral dysfunction[47].

In recent studies, an interaction between genetic risk of inheriting schizophrenia and schizotypal symptoms has been observed in many neurocognitive functions. The schizotypal symptoms are related with deficits in the verbal and visospacial memory, complex attention and execution function only among individuals who have an elevated genetic risk of suffering schizophrenia. The presence of schizotypal symptoms together with a familial background of schizophrenia seems to place the subjects with a greater risk of suffering certain cognitive deficits that suggest that some neurocognitive functions may be sensitive to subpsychotic symptoms within the schizophrenia spectrum. This would be consistent with a model in which genetic sites for both schizotypal symptoms as well as neurocognitive deficits participate[58]. The memory deficits of visospacial work have been related with the DISC1 gene59, that has been previously identified as a susceptibility site for schizophrenia[60].

Finally, investigations that relate cluster A with the genes of the neurotransmitters and their receptors are reflected (table 3).

Cluster B

The antisocial personality disorder (APD) and the borderline personality disorder (BPD) are the only cluster B PD in which their heritability and genetics have been investigated.

Antisocial personality disorder

The appearance of new techniques and interventions that may improve their treatment and even have a repercussion on the legal aspects is greatly hindered by the controversy regarding the etiology and course of APD. At present, the importance of the genetic aspects in the attributability of the criminal acts of individuals with this disorder are currently being discussed. Dinwiddie concludes that although it is convenient to go deeper into the genetic research techniques, greater knowledge of the cause of the disease does not necessarily have to alter a guilty sentence[64]. Antisocial behavior and altruism are not opposite poles of the same dimension but rather independent tendencies with different etiologies. Thus, it is not sufficient to create intervention strategies for the antisocial behaviors. It is necessary to promote desirable and prosocial behaviors[65]. To establish an APD diagnosis, there must be a previous background of dissocial disorder, prior to 15 years of age, that implies a repetitive and persistent behavior pattern where the rights of others are not respected and the social rules imposed for the adults are violated. There are studies that measure antisocial behavior by means of criminality

Table 3 Molecular genetics and cluster A personality disorder

Authors	Results
Kestler LP, 2000[61]	Cluster A is associated with low DA2 dopamine receptor density
Rosmond R, 2001[62]	DA2 receptor deficit could elevate blood pressure by a deficient inhibition in catecholamine release. The homozygotic subjects for T allele the D2 dopamine receptor (DRD2) exon 6 present a higher blood pressure and more PB than cluster A in comparison with the remaining alleles
Blum K, 1997[63]	Strong association between Taq A1 allele of the D2 dopamine receptor with schizoid/avoidant behavior. Weaker association between 480-bp VNTR 10/10 allele of DAT1 dopamine transporter gene and schizoid/avoidant behavior

and delinquency, although these by themselves do not imply an APD. The difference between both terms is found in that criminality is a timely act that entails arrest, sentencing or jail while delinquency refers to persistent illegal acts over time[66]. The epidemiological data published by Robins and Regier indicate that only 27% of boys and 21% of girls with three or more dissocial disorder symptoms will be diagnosed of APD in the adult age. If there are six or more symptoms, then the percentages increase to 49% and 33%, respectively. Delinquency before 15 years of age predicts APD in 29% of the men and 13% of the women[67]. These studies suggest that a diagnosis of dissocial disorder does not assure the subsequent presence of APD.

Applying the principal personality models to the APD, some traits that underlie said disorder can be established. Using a tridimensional scheme, Eysenck found high scores in psychoticism and extraversion[68]. Also based on a tridimensional scheme, Cloninger found high scores in NS and low scores both in RD and HA[2]. Considering that there is a genetic component in all these personality dimensions, the existence of temperamental factors of APD can be indirectly deduced[69]. Other authors have already suggested a number of personality variables that may share common genetic influences with antisocial behavior, such as low HA, high NS, low RD and others[70].

Antisocial behaviors are so diverse that even their etiology may be different. It has been observed that genetic influences are significant in crimes against property but not for violent crimes with presence of alcoholism[71]. Cloninger studied this phenomenon in Danish twins and suggested a different etiology for these behaviors as there is no genetic coincidence[72].

According to the psychobiologic model of Siever and Davis the personality traits only cannot precipitate an APD and only the interaction of biological and psychological risk factors can be responsible for its appearance[73]. Furthermore, social factors should be added so that the risk of suffering APD would increase considerably in those individuals who are vulnerable due to their personality traits, who are exposed to antisocial behaviors of their parents and chaotic family settings[69]. These authors have proposed that APD could be associated with a combination of impulsiveness (regulated by lower serotonin levels) with elevated behavioral activation (regulated by high mono amine levels)[73]. Thus, it is difficult to elucidate what importance genetic, psychological and social factors have, both separately as in interaction with others and if any of them is sufficient to establish a causality.

There is evidence that oppositional defiant disorder progresses to dissocial personality disorder as age increases but it should be clarified that many children with oppositional defiant disorder do not evolve to a dissocial disorder. Men are more affected than women by the dissocial disorder, but there are no consistent data that suggest the same for the oppositional defiant disorder[74]. Studies in adults, who were diagnosed with dissocial disorder in childhood, show that one to two thirds of the adult age subjects have psychiatric disorders, personality disorders or significant criminality[75,76]. Moderate comorbidity with anxiety and mood disorder and a strong relationship with attention deficit hyperactive disorder (ADHD) has been seen[74], with one third of the cases of ADHD developing significant criminality[77,78]. However, there are no studies on the proportion of adults with APD and previous background of ADHD[69].

Studies on heritability in dissocial and oppositional defiant disorders show a wide range of variation. The information received from different informers in the same study has revealed that the heritability grade varies greatly. Specifically, the information received from the adolescents themselves showed much less heritability[74]. On the contrary, the information from the parents led to the conclusion of low heritability but one having a greater influence from the shared environment than self-report based studies[79]. Studies on adoption only suggest less familial influences in antisocial behavior than studies on twins and adopted siblings. However, the last two do not show significant differences between them[66]. Heritability grade varies from 7% to 81%, so that it is very difficult to reach firm conclusions. Three of the studies with larger sample suggest that most of the measurements of antisocial behavior in childhood reveal 50% heritability or one that is even slightly greater[74].

There is a genetic polymorphism in the dopamine receptor D5 gene that correlates with the antisociality indexes. This suggests that there is an association between this receptor and severity of the oppositional defiant disorder in both genders. The relationships of this same polymorphism and the APD are positive in the case of women but not so in men[80]. However, Cloninger and Gottesman indicate that the genetic influences are minimum in juvenile delinquency and that the peer group pressure has the greatest influence[72], this affecting monozygotic twins more than dizygotic ones[81]. This statement is affected by the possibility that it is the individual him/herself who chooses to belong to a peer group with antisocial behaviors. Therefore, there would be genetic influences in the relationship between antisocial behavior and selection of peer group[81]. Taylor even indicates that the subjects who begin to manifest antisocial behaviors first have a more antisocial peer group than those who begin to manifest them later[82].

Currently, the research lines in molecular genetics are being developed on the ADHD and APD in relationship with alcohol and/or substance abuse (table 4).

Genetic studies on alcohol abuse have followed two aspects: on the one hand, that related with the genes that participate in alcohol metabolism. It is unlikely that these would throw any light on the antisocial behavior in childhood. The second aspect examines mono amine genes and may be more revealing[74]. Regarding abuse substances, a study of 197 adopted subjects found biological differences between men and women. It was observed in the men that

Table 4 Molecular model and antisocial personality disorder

Authors	Results
Thapar A, 1999[83]	Influence in ADHD of the D4 dopamine receptor genes (DRD4) and dopamine transporter (DAT1)
Reich T, 1998[84]	Relationship between tendency to alcohol dependency and genetic markers D4S244 and D4S2393
Stamps VR, 2001[85]	In a single family, with mild mental retardation and elevated aggressivity, a mutation of the monoaminoxidase gene was observed in the chromosome X of the males
Lappalainen J, 1998[86]	Regarding the low levels of serotonin metabolites in aggressive and impulsive individuals, vulnerability in the 5HT1B receptor gene is suggested
Sander T, 1998[87]	In aggressive and impulsive individuals, no differences are observed in the serotonin transporter gene
Slutske WS, 2001[8]	It is suggested that there is at least one genetic site that increases the vulnerability to suffer APD together with pathological gambling, dissocial-pathological gambling disorder and adult antisocial-pathological gambling behavior
Vanyukov MM, 1998[89]	Association between the D4 dopamine receptor gene and tendency to substance dependence and NS, this association being strong in women
Sunahara RK, 1991[90]	D5 receptor shows ten times more affinity with dopamine than the D1 receptor
Vanyukov MM, 2000[80]	A high density of the D5 receptor is detected in the brain structures of the limbic system, which may indicate the intervention of this receptor in emotional regulation

when the alcohol abuse was observed in the biological parents, this had a direct effect on substance abuse in descendents and that antisocial personality of the biological parents increased the risk of childhood aggression initially, with subsequent evolution towards dissocial disorder and substance abuse. However, in women, the antisocial personality of the biological parents was directly reflected in a dissocial disorder, but not through aggression. In both men and women, an adverse setting had a direct effect on aggression, this increasing the risk of substance abuse[91]. All this is due to the fact that not only the effects of genetic transmission have an influence in the parent-child relationships but also the style of upbringing and the behavior itself of the parents. It has also been observed that men with APD have five times more likelihood of having substance abuse than those who do not have it, but in women, this risk is twelve times greater with the presence of APD than without the presence of this disorder[67].

Regarding studies in twins, it is important to analyze age in relationship to the possible genetic and environmental influences in antisocial behavior (table 5).

Table 5 Studies of twins and antisocial personality disorder

Authors	Results
Matheny AP, 1989[92]	From 12 to 30 months of age, monozygotic twins show more concordance in changes in emotional tone, fear and approach than the dizygotics
Miles DR, 1997[79]	Regarding aggression, the evolutive process from infancy to adult age, weight of the shared environment influences decreases and the weight of the genetic influences increases
Rhee SH, 2002[66]	Juvenile delinquency during adolescence, on the contrary to criminality in the adult age, is moderately affected by genetic influences but strongly affected by shared environment. Antisocial behavior at early ages that persists during the life time is inheritable and is less affected by environmental influences than antisocial behavior that initiates in later ages or is only limited to childhood or adolescence
Lyons MJ, 1995[93]	Heritability of antisocial traits in adults is higher in the young subjects

Finally, it should be emphasized that the antisocial behavior studied has greater prevalence in men than in women. Thus, it is necessary to evaluate if the magnitude of the genetic and environmental influences differs between men and women. The scientific literature shows that genetic and environmental influences are the same for both genders[66], although Miles and Carey found that the genetic influence in aggression was slightly higher in men than in women[79].

Borderline personality disorder

The essential characteristic of the BPD is a general pattern of instability in interpersonal relationships, self-image and affectivity, and significant impulsivity that begins at the onset of the adult age and occurs in different contexts[29]. Although it is admitted that BPD has a complex multifactorial etiology, the genetic substrates of this disorder have not been extensively investigated.

Many clinicians have maintained that BPD is mainly a product of environmental risks that go from aversive childhood experiences to organic traumas. Kernberg proposed that the principal nucleus of this disorder consisted in an innate manner of managing situations that was too intense and aggressive together with an innate deficiency in the capacity of tolerating anxiety[94]. However, other relevant authors suggest that the base of BPD is an inherited biological predisposition to emotional unbalance[95]. This imbalance increases sensitivity to emotional stimuli, causes intense reactions to these stimuli and a slow and delayed return to a normal emotional level. The research lines do not only imply that the biological factors are the only determinants of the disorder but also that environmental factors are necessary to develop it. However, the behavior that lasts over time could have a biological coding of some type[96].

Regarding heritability of BPD, studies in twins show contrasting conclusions: a first study points to the environment as the factor having the most importance for the development of BPD while the second, with a larger sample, points to the fact that the genetic effect was emphasized, the proportion of the variance explained approaching 0.70[97].

The group of familial studies supports the heritability of BPD as a diagnosis but the genetic base could be stronger for some of its dimensions such as impulsivity/aggression and emotional instability than for the diagnostic category itself. Thus, these dimensions could represent inheritable endophenotypes that would significantly contribute to an increase in the likelihood of developing a BPD[98].

At present, significant evidence exists for the familial transmission of BPD or of traits that form part of that disorder due to the greater frequency of the diagnosis in relatives of subjects with BPD than in relatives of subjects who do not have this disease. In a 1985 investigation, it was observed that familial transmission of BPD is especially low when the subjects have a schizotypal personality disorder in comorbidity with BPD[45]. However, the dominant characteristic of the genetic studies of BPD is the variability of the frequency of presentation of the disorder among first degree relatives, probably as a consequence of the different definitions of the disorder and whether the patient's relatives are interviewed[45,99,100].

Some studies have investigated the correlations between BPD and the model of the five important personality factors, these being: neuroticism, extraversion, openness to experience, thoroughness/scrupulosity and amiability/friendliness. Neuroticism correlates highly and positively with BPD, with a mean correlation of 0.5. Thoroughness/scrupulosity does so with a mean correlation of -0.23 and amiability/friendliness with a mean correlation of –0.24. Correlations of extraversion and openness to the experience are practically null[97]. Based on these data, almost half of the variance in BPD is explained by this personality model. In this way, the genetic analysis of the five factors of the model may help to clarify the genetic bases of BPD[97].

There are investigations prior to those conducted by Torgensen in the year 2000 that establish that the individuals who score high on a dimension similar to neuroticism have the short variant of the serotonin transporter gene promoter region. The serotonin transporter (5-HTT) is coded by a single copy gene (SLC6A4) located in chromosome 17q12. This gene has a polymorphism in its regulatory region, called 5-HTTLPR, that is characterized by presenting a variable number of tandem repeats of 44-bp (short or long allele depending on the number of tandem repeats), that finally conditions the protein transcription level. This polymorphism accounts for 3% or 4% of the total variance and 7% or 9% of the inherited variance[26]. In a similar study, it was seen how the gene that codifies the D4 dopamine receptor has an influence on the high scores in novelty seeking and low ones in awareness[7]. Although the studies explain a very low percentage of the total variance, they are a first step towards untangling the gene mapping responsible for PD. In an investigation conducted by Livesley, 18 personality dimensions were described that justified many of the abnormalities present in the PD. Among these dimensions, the following ones are very similar to aspects of BPD (the subtraits are listed between brackets): affective lability (affective instability, exaggerated reactions, generalized hypersensitivity, rage and irritability), cognitive dysfunction (depersonalization, schizotypal cognition and brief stress psychosis), identity problems (anhedonia, feelings of emptiness, labile self-concept and pessimism), involvement of insecurity (separation protest, feared loss, proximity seeking and intolerability of aloneness) and suicide (suicidal ideas and attempts). Affective liability, identity problems and involvement of insecurity, characteristic traits of BPD, belong to an upper order of factors called lability or affective dysregulation. In that investigation, an approximate heritability of 0.4 to 0.5 was found for the traits, subtraits and up-per factors. Livesley proposes that the lability or affective dysregulation dimension is the nucleus of BPD, since most of the variance seems to be due to this factor[101].

Due to the elevated potential danger supposed by high impulsivity in a relationship with the suicide attempts and mortality in these patients as well as the comorbid diseases they have, there are several studies that analyze these aspects, their relationships with the neurotransmission systems and their heritability (table 6).

It must be remembered that suicidal behaviors have been related with lower opiate activity, so that these behaviors would reestablish adequate levels of endogenous opiates. Plasma encephalin levels directly correlate with the severity of suicidal behaviors in patients with BPD[106]. Most of the studies suggest the relationship between an intronic polymorphism in the tryptophan hydroxylase gene and suicidal behavior. Specifically the U allele of this gene has been associated with persistent aggression in the non-psychiatric population[107].

Finally, the disorders that are most frequently found in the relatives of subjects with BPD must be kept in mind in case any relationship can be established with them. Greater family risks of impulsivity or of affective personality traits, but not of both, have been observed[108]. The relatives of subjects who have BPD have a significantly greater proportion of bulimia, greater tendency to substance dependence abuse, mood state disorders and greater proportion of the three clusters PD than the relatives of subjects not diagnosed of this disorder. However, these differences do not appear in the relatives of subjects with depression, the general pattern of disorders being similar. This may indicate an overlapping of the etiological factors. Therefore, from a genetic-familial perspective, if the BPD is a form of mood disorder, it would be an attenuated form. The individuals with comorbidity of BPD and mood state disorder would be those having the greatest genetic vulnerability, followed by the subjects only with the mood state disorder and finally the subjects with only BPD[109]. These results reveal the family relationship between BPD and mood state disorders but do not demonstrate that it is a specific relationship of the BPD, since other PD also have these relationships.

Cluster C

In the current scientific literature, few specific works have been found on the genetics of the C cluster. This group includes avoidant personality disorder (APD), dependent personality disorder (DPD) and obsessive-compulsive personality disorder (OCPD)[29].

In a recent epidemiological study conducted in the United States of America, the most prevalent personality disorder in the general population was OCPD, locating the APD and DPD in fifth and seventh place, respectively[110]. Therefore, knowledge about the genetic substrates underlying these PDs is important in order to attempt to improve the interventions on the persons who suffer them. The results of the molecular genetic studies in cluster C are summarized in table 7.

Given the comorbidity among PD of cluster C, anxiety and affective disorders[116], and the evidence of its modulation through the common genetic factors[117], it is possible that, among the different PD, the predisposition to suffer any of those included in cluster C is more strongly influenced by environmental and experiential factors, whose impact on the brain could be under genetic control[113].

CONCLUSIONS

From the clinical point of view, going into the genetic aspects of personality and its disorders in greater depth can mainly be useful for two reasons: to influence future diag-

Table 6 Genetics and suicide

Authors	Results
New AS, 2001[102]	In the subjects with a background of suicide or high levels of impulsivity and aggressivity, there is a polymorphism of chromosome 11 that may be manifested in lower levels of serotonin metabolite in cerebrospinal fluid
Oquendo MA, 2000[103]	Most of the investigations indicate lower serotoninergic activity in BPD patients but the lower levels of this metabolite have been found in depressed suicide attempters without comorbid pathology of BPD
Roy A, 1983[104]	Low levels of serotonin together with deficiencies in the dopamine system are related with suicidal behaviors in patients with BPD and depression. Evidence of genetic risk factors in suicide has been found in family studies, of twins and adoptions
Siever LJ, 1992[105]	A relationship between the noradrenergic system and assumption of risks, irritability and impulsivity has been suggested. This more intense reaction towards the environment together with increase of tendency to impulsive aggression, regulated by the serotoninergic system, may be combined to create the problematic behavior pattern observed in patients with BPD

Table 7 Molecular genetics and cluster C personality disorders

Authors	Results
Joyce PR, 2003[102]	Association between the DRD4 exon III polymorphism with the 2-repeat allele and obsessive and avoidant symptoms was found. The same association was observed in the –521 C>T polymorphism. It was also detected that 30% of the subjects with C,C genotype presented a OCPD versus 4% of individuals without this genotype. The Gly9,Gly9 genotype of DRD3 was associated with more obsessive symptoms and with the OCPD
Jönsson EG, 2003[112]	No associations were found between the DRD3 variants and certain personality traits
Jacob CP, 2004[113]	No differences were found in the genotypal distributions of 5-HTTLPR among control subjects, subjects with cluster B PD and subjects ion cluster C PD. Within the cluster C, carriers of the 5-HTTLPR short allele showed higher levels of neuroticism and harm avoidance
Davidson RJ, 2002[114]	In the cluster C PD subjects, carriers of low activity alleles of 5-HTTLPR, the anxiogenic stimuli may cause potentiation in hyperexcitability of the amygdala, or the physiological activity of said brain structure may decrease control exerted by the prefrontal cortical circuits due to increase of neurotransmission
Samuels J, 2000[115]	Subjects with obsessive-compulsive disorder (OCD) have greater rate of prevalence of cluster C PD in general and of APD and OCPD in particular (15% and 32%, respectively). It has been identified that high neuroticism and OCPD are more frequent in relatives of subjects of OCD than in those of control subjects, so that the OCD and OCD could be alternative expressions of the same underlying vulnerability

nostic classifications and to influence the ability of the prescribing clinicians to modify biological aspects (for example, acting on the neurotransmission systems) with external agents such as psychopharmaceuticals.

To do so, we should consider a series of limitations and contributions that have been found in this review. On the one hand, it should be emphasized that not all the PDs have been studied equally. Genetically, the investigation mainly revolves around BPD and APD due to their high comorbidity with other disorders and the social repercussion of violence and aggressivity. Cluster A disorders have been studied genetically to a lesser degree and an attempt has been made to reveal aspects of the schizotypal personality disorder (STPD) only because of their close relationship with Schizophrenia. Many more genetic investigations are necessary and even more in regards to schizoid and paranoid personality disorders whose bases or genetic relationships are not clearly known as occur with the PDs of cluster C and the remaining PD of cluster B.

It seems to be clear that no single gene is responsible for a specific psychiatric disorder and that the diversity of genes, especially in the personality disorders, is essential to understand the role of genetics. In order to know the role of genetics and environment in Personality Disorders, homogeneous studies and their replication are necessary to achieve an adequate consistency of the results. To reach this objective, using the same diagnostic criteria, similar age of the samples (since the influence of the genes varies with age) and a sufficient sample size is essential.

From the genetic point of view, there are different reasons that explain the absence of replication of these studies. Complex inheritance diseases, such as these, are the result of the contribution of many small or moderate effect genes. The power of a single study to detect this effect is very low so that it is not surprising that it is difficult to replicate the findings. In addition, the genetic mutations may differ in frequency and effect in the different populations. Even the interactions with the environment differ according to the population. Finally, one of the most important causes for the absence of replication is the inexactness in the clinical criteria used in psychiatry. In this sense, the need to refine and use endophenotypes has been stressed in recent years. However, these seem to be qualitatively insufficient to facilitate the integration of the knowledge derived from the evolutionist theories of the mind and its psychopathology.

The dimensional models such as that of Cloninger's personality one seem to be useful to join genetic and endophenotype aspects with the current clinical classifications. Thus, very conclusive results have been obtained in regards to the heritability of temperament. In turn, it has been possible to relate this with certain personality disorders when it has not been possible to relate them directly with genetic aspects.

Regarding the diagnosis, this review makes it possible for the clinicians to consider the possibility of taking the personality dimensions into account. Thus, these could be considered as interphenotypes given that they are half way between the genes-endophenotypes and the current clinical

classifications. These interphenotypes or personality dimensions are useful to reach the diagnosis since they could induce suspicion on it. However, they could also be taken into account due to their utility to better understand possible patient subgroups within a same diagnosis. In this regards, APD and BPD with the Cloninger dimensions or with the impulsivity dimension and their genetic correlates are examples. Along this line, the authors of this present review are conducting a study that aims to use Cloninger's dimensions as interphenotypes that help the clinician to determine if a patient with a probable diagnosis of PD according to the DSM-IV-TR is more consistent with the subject group without diagnosis or with that of the positive disorder.

However, it seems that we are still far from being able to include genetic markers or even endophenotypes in the diagnostic classifications of the personality disorders.

Regarding treatment, these personality dimensions (temperament) as genetic correlates (interphenotypes) may be useful for the clinician when choosing a drug that influences the neurobiological system that is partially coded by a certain group of genes. In this way, the use of drugs that intervene in the dopamine system for the treatment (or modulation) of dimensions such as novelty seeking of the Cloninger model or impulsivity in patients with APD or BPD and the use of antidepressants due to the influence on the serotonergic system, etc. takes on greater importance.

Equally, these interphenotypes should be taken into account when choosing a drug to approach other disorders related with these temperament dimensions, both in adolescence (attention deficit-hyperactivity disorder) as in the adult age (dual disease).

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