The genetics of child temperament

J. Ivorra-Martínez [a], J. Gilabert-Juan [a], M. Moltó-Ruiz [a], J. Sanjuán [b]

THE GENETICS OF CHILD TEMPERAMENT

Summary. Introduction. *In spite of the high initial expectancy in preliminary results concerning the genetics of personality, these studies have not provided satisfactory results. The failure could be related to the lack of biological validity of personality concept and the important influence of environmental factors on personality. A possible way to solve this problem is to look at the temperament of preschool children. It is expected that variability in infants' behaviour can be better defined and with less environmental influence.* Development. *Firstly, twin and adoption studies of child temperament in comparison with the studies of personality in adults are reviewed. Secondly, the molecular association studies carried out concerning child temperament are analyzed. The serotonin transporter gene (*5-HTT*), D4 receptor gene (*DRD4*) and mono amino oxidade-A gene (*MAOA*) have been considered candidates to explain variability in child temperament because these genes have been related with specific personality dimensions and mental diseases. Finally, the methodological problems and the future direction of research in this field are considered.* Conclusions. *Heritability shows higher values in infant temperament than in adult personality. Different gene polymorphisms on* 5-HTT, DRD4 *and* MAOA *could explain some individual variability in children's behavior, although replication studies are needed to confirm the role of these genes. Longitudinal studies in large samples that include gene and environmental interactions are one of the best ways to improve our knowledge about the genetics of child temperament. [REV NEUROL 2007; 45:]*

Key words. 5-HTT. *Association studies. Children.* DRD4. *Genetics.* MAOA. *Personality. Temperament.*

INTRODUCTION

Personality is usually understood as stable patterns of response in individual behaviour. Although this could be the most written about topic in Psychology, the existence of these patterns and the validity of the personality concept itself have both been questioned [1]. Nevertheless, the study of the origin of the behavioural stable patterns and, particularly the debate about its aetiology (genetic vs environmental factors), has been one of the most controversial issues in the research history of Psychology [2]. The advent of molecular genetics has increased the interest in this field because new and powerful methodologies have been applied to study personality. However, in spite of the amount of studies carried out, the expected results have not been achieved. In a clinical point of view, the importance of research of biological bases of personality arises from the hypothesis that suggests several mental diseases could represent the limits of different personality dimensions [3-5].

Personality is a difficult concept to define so the study of their genetic basis constitutes a great deal. There are several crucial disadvantages in this type of study, the most important being, the enormous influence of environment on this trait. From a genetic point of view, personality is understood as a multifactorial trait with probably several genes involved, each one likely having a weak effect. In addition, these genes will interact between themselves and with several environmental factors. In fact, environment has a higher percentage of total variability in personality than genes. This explains why the results obtained up to now have been controversial and relatively poor in spite of the great effort carried out.

In order to solve this problem, the analysis of traits closer to biological basis rather than personality, such as temperament, has been proposed. Temperament could be defined as individual differences in behaviour trends, which are stable and have a constitutional base. While personality would be established during adolescence, temperament is supposed to appear at birth and, therefore, would have fewer environmental influences. It has been suggested that personality would be a development between environmental factors and temperament throughout life [8]. Environmental factors, some of them intrauterine [9], must be also significant in temperament, but it is well established that environmental factors are more involved in personality than in temperament.

There are many models which try to define the temperament dimensions, and some of them offer scales to measure them. In adults, the most used model in genetic studies has been Cloninger's psychobiological model [10] and its TCI and TCI-R scales (and previously the TPQ scale) [11]. According to this model there are seven main dimensions in personality, four of which are considered temperamental dimensions: 'novelty seeking', 'harm avoidance', 'reward dependence' and 'persistence'. The main interest in this model in genetic studies is because it associates the different dimensions to specific biological systems: dopaminergic system to 'novelty seeking', serotoninergic system to 'harm avoidance' and noradrenergic system to 'reward dependence'. But temperament in adults has an important disadvantage: it's very difficult to separate it from personality. In fact, Cloninger's model has been criticized because its temperamental dimensions overlap with personality dimensions of other scales. As an example, the temperamental dimension 'harm avoidance' is very close to personality dimension 'neuroticism' [12]. This fact has meant that genetic studies of temperament in adults suffer from severe replicability failure, in a similar way to what happens in studies using the personality scales [13].

An alternative to adult temperament is to study temperament in children, because it is well defined and clearly differentiated from personality. In children there are also several models

Accepted: ??.??.??.

[a] Human and Molecular Genetics Laboratory. Genetics Department. Biology Faculty. Valencia University. Burjassot, Valencia. [b] Psychiatry Unit. Medicine Department. Valencia University. Valencia, Spain.

Corresponding author: Dr. Julio Sanjuán. Unidad de Psiquiatría. Facultad de Medicina. Universidad de Valencia. Blasco Ibáñez, 15. E-46010 Valencia. E-mail: julio.sanjuan@uv.es

Versión española disponible en www.neurologia.com

trying to explain temperament, and most of them define dimensions very close to biological features, such as reactivity level to stimuli. Traditionally, the most used scales have been the following three: EASI Temperament Survey [14], Colorado Child Temperament Inventory [15] and Infant Behaviour Record [16]. But there are other scales that have gained importance such as the Neonatal Brazelton Scale Assessment (NBAS) [17], because is not just filled in by parents, but have a section which is completed by trained observers, too.

TWIN AND ADOPTION STUDIES

The first question we should ask is if a child's temperament really has an important hereditary component and therefore should genetic studies be undertaken. In order to answer these questions two strategies have been traditionally carried out: twin and adoption studies.

Twin studies have been the most used method, and they are based in correlation comparisons between monozygotic and dizygotic twin pairs. Monozygotic twins are genetically identical clones, while dizygotic twins share half their genes on average, the same as any pair of siblings. Genetic characters should therefore show higher concordance in monozygotic compared to dizygotic twins, and many characters do. With respect to temperamental dimensions, most of them also show higher similarity in monozygotic than in dizygotic twins [18]. Historically, this field has been influenced by data obtained in the New York Longitudinal Study [19], where a higher significant correlation in monozygotic (around 50%) rather than dizygotic twins (around 15%) is found in several temperamental variables. Other later studies have obtained similar correlations with variables like emotionality, attention and activity [20,21]. Generally, heritability values are between 40 and 60%, which support an important contribution of the genetic variance to the variability of the trait. However, we must note that all these studies showed very low correlation values in dizygotic twins, or even negative values. An explanation of these results can be found in the way the questionnaires were filled in, mainly by the parents who tend to exaggerate differences between dizygotic twins more than in monozygotic twins.

In studies using scales which measure personality, heritability is about 30% [2], a lower value than temperament measures. This should be expected, because personality has *a priori* higher environmental influence than temperament.

Twin studies show some disadvantages:

- Monozygotic twins tend to share not just more genes but also more environmental factors than dizygotic twins, so greater similarity could be due to these factors.
- Monozygotic twins separated at birth and brought up in separate environments would provide the ideal experimental conditions, but there are very few of them.
- There is a bias of ascertainment because twins who are very different are less newsworthy than markedly similar twins.
- Research on twins cannot distinguish intrauterine environmental factors from genetic factors.

Adoption studies are less frequent than twin studies and they show small samples. The main obstacle in this type of study is the lack of information about biological families. These studies are based in the comparison of a trait between adopted children and their biological and adoptive family. If the observed variability in the trait has a genetic influence, a higher correlation is expected between adoptive children and their biological family than between the children and their adoptive family. These kinds of studies usually obtain lower heritability values than twin studies, around 40% [22]; also in some cases no evidence of genetic variability has been found [23]. Braungart et al [23], using the Infant Behaviour Record scale in an adoption study, got similar results for each temperamental variable to a previous twin study which used the same scale [25].

Twin as well as adoption studies show both a significant variability in their results. The main reasons could be found in the different scales used to measure temperamental dimensions (these scales show similar but not identical variables), and the large range of ages of the individuals studied, from three months to adolescence. In spite of these limitations, it has been concluded that genes contribute to temperament variability in childhood. This contribution has been quantified between moderate and significant.

ASSOCIATION GENETIC STUDIES

The second question we should ask is which specific genes are involved in child temperament. To answer this, association studies have been mainly carried out. In a typical association study, there is a comparison between frequencies of genetic variations of candidate genes (alleles) in two different samples belonging to the same ethnic group or population: people showing the trait are compared with people without it. This comparison can reveal the existence of positive association between an allele (or allele combination) and the trait if a significantly higher frequency is found of that allele in the first group of people in comparison with the second group.

In 1996 two papers about the genetic basis of personality were published which aroused great interest in this subject. One of them linked the *5-HTT* gene with anxiety-related traits [26], and the other one was an association study between *DRD4* gene and 'novelty seeking' [27]. Both of these studies got positive results and were of special interest because they supported Cloninger's psychobiological model. 'Novelty seeking' dimension was related with the dopaminergic system and 'harm avoidance' dimension (indirectly related with neuroticism and anxiety) with the serotoninergic system. Unfortunately, this initial success has not been maintained, and even the results from these two studies have subsequently been questioned. After this, we will revise the studies carried out in these and other biological systems applied to the study of children's temperament (Table).

The serotoninergic system is widely distributed in the nervous system, with critical roles in many functions such as neurogenesis and neuronal plasticity. The *5-HTT* gene (officially *SLC6A4*) encodes the serotonin transporter, whose function is the recovery of serotonin released to the intersynaptic space. This gene has 15 exons and it shows high evolutive conservation in the transcriptional control region at the beginning of the gene (5'-extreme) and in the exon/intron organization [28]. This gene has been closely studied in relation with anxiety and neuroticism traits, depression and adult temperament, specifically with the Harm Avoidance dimension [27]. Several of these studies showed significant results, but others could not replicate the positive results using independent samples [29,30].

In children, *5-HTT* has been less studied, and the genetic analysis has been focused on the *5-HTTLPR* polymorphism, a

Table. Molecular genetics studies on child temperament.

Study	Sample	Scale	Genes	Association
Ebstein et al [33] [a]	81 two-week- old children	*Neonatal Brazelton Scale Assessment*	*5-HTT, DRD4*	*DRD4 + 5-HTT,* with 'neuroticism' and 'harm avoidance'
Auerbach et al [34] [a]	81 two-month- old children	*Rothbart's Infant Behavior Questionnaire*	*5-HTT, DRD4*	*DRD4 + 5-HTT,* with 'negative emotionality' and 'distress to limitations'
Lakatos et al [36]	90 one-year-old children	Report of the mother, study of videos of the child	*5-HTT, DRD4*	*DRD4 + 5-HTT,* with stimuli provoking anxiety
De Boer et al [43]	29 children with the Soto's syndrome	*EASI Temperament Survey*	*NSD1*	*NSD1,* with less irritable temperament
Beitchman et al [37] [b]	77 five to fifteen year-old children	Measurements of aggressiveness	*5-HTT*	*5-HTT,* with infantile aggressiveness
Kim-Cohen et al [44] [b]	975 seven-year-old children	Measurements of antisocial behaviour and response to the mistreatment	*MAOA*	MAOA, interaction with environmental factor mistreatment

[a] The same sample was used in both studies; [b] In these studies variables of temperament were not considered but variables related to it.

VNTR (variable number of tandem repeats) microsatellite located at the 5' transcriptional regulation region of the gene. The *VNTR* shows two types of alleles: the *l* allele (with 16 repeats) and the *s* allele (with 14 repeats) with functional differences because the short allele has a lower level of transcriptional expression compared to the long allele [26].

The dopaminergic system has been related with motor functions, emotions and pleasure feelings. The most studied gene in temperament has been *DRD4*, which encodes for a G protein-coupled dopamine receptor. The analysis of this gene, with 4 exons, has focused in a 48 pb *VNTR* located in the third exon which can vary between 2 and 11 repeats [31]. This *VNTR* has been associated with different personality traits and adult temperament, mainly 'novelty seeking' of Cloninger's model [27], as well as mental diseases such as attention-deficit hyperactivity disorder [32]. In all these papers, the different *VNTR* alleles have been grouped into two types: short allele when carrying 2-5 repeats, and long alleles when carrying 6-11 repeats.

An interesting longitudinal study trying to associate both genes (*5-HTT, DRD4*) with temperamental variables was performed. The variables were measuring at two weeks (using the NBAS scale) [33] and at two months (using the Rothbart's Infant Behaviour Questionnaire) [34] in a sample of 81 children. An association was detected between the longest alleles of the *DRD4 VNTR* and several temperamental variables measured at two weeks such as 'orientation'. This variable could be related with 'novelty seeking' in adults [35]. For 5-*HTT* no positive results were obtained applying the univariant analysis. However, when both genes were considered at the same time, it was found that the homozygotes *ss* for *5-HTTLPR* carrying in addition the short variants of *DRD4 VNTR* showed significant lower values in Orientation. When temperament was measured at two months, this association between both genes was also found. At this time the univariant analysis with the *5-HTTLPR* also gave a positive result. This could be explained if the genes involved in temperament are different (or they have different roles), while temperament evolves with age.

Lakatos et al [36] carried out a study with 90 one-year-old children. They asked mothers, as well as taking direct observational measures about variables similar to novelty seeking of adults. The purpose of this work was to associate these variables with *5-HTT* and *DRD4*. Any association with mothers' answers was found (it could be explained by the bias of questionnaires filled in by parents) while from the observational data a *DRD4 VNTR* effect on children's behaviour in response to the presence of a stranger was found: the long alleles of the *DRD4 VNTR* were associated with lower anxiety values in reaction to the stimuli. Besides, this polymorphism was again modified by *5-HTT*, because the presence of the *5-HTTLPR-s* allele significantly increased children anxiety independently of the *DRD4* genotype.

The *5-HTT* gene has also showed significant association with aggressiveness in children [37]. The *s* allele of *5-HTTLPR* (in combination with a low transcriptional allele of *rs25531*, another functional polymorphism located in the promoter of 5-HTT) is associated with increased aggressiveness.

Although *DRD4* and *5-HTT* have been considered the most promising candidates to explain the variability in the different temperament dimensions, there are many other genes that could be involved in this trait. Genes of the dopaminergic system like *DRD2*, *DRD3* and *DAT1* have been studied in adults, trying to associate them with different personality dimensions such as neuroticism [38-40]. Genes of the serotoninergic system such as *5-HT1A*, *5-HT1B*, and *5-HT1C* have been also studied with respect to their involvement in adult temperament [41,42]. All these studies showed negative results, or when positive could not been replicated. At present, these genes have not yet been analyzed in children's temperament.

The Sotos syndrome gene (*NSD1)* has also been associated with temperament variability [43] because patients with the mutated gene (deletions and point mutations in the coding region) are less irritable than controls. This study has been carried out in children of different ages (3 to 18 years), but the sample was very small (just 29 people), and therefore it needs to be reproduced in wider samples before assuming a likely role for this gene.

Genes coding enzymes which metabolize different neurotransmissors have been studied in mental diseases and in behaviour. An example is the MAOA enzyme (monoamine oxidase A), that degrades selectively serotonin, norepinephrine and dopamine previously recruited to presynaptic neuron. A study in a sample of 7-year old Caucasian children [44] showed that high activity

allelic variants of MAOA increase the probability of: suffering mental disorders; antisocial behaviour and attention/ hyperactivity deficits. Besides, some gene variants were associated with children's responses to domestic violence. These kinds of studies highlight the importance of gene-environment interactions, because the contribution of both factors is fundamental to identify the mechanisms operating in temperament, behaviour and personality development.

PERSPECTIVES AND FUTURE DIRECTIONS

Complex traits like temperament represent a challenge for genetic studies. In order to advance in this field several ideas have been suggested.

Increasing of statistic power in genetic studies

One of the most difficult phases when working with children is to get representative samples with a high enough number of individuals. This aspect is harder in children than in adults. Currently, very few studies have a sample of over 100 children. This makes it very difficult to detect genes with moderate or weak effects. Consequently, it will be necessary to increase the sample in future studies. In this way, the implementation of massive genotyping technologies (MassArray ®, BeadArray ®, TaqMan ® technologies as well as the use of tag-SNPs), will quickly increase the number of genetic polymorphisms studied, making it easier to analyze many candidate genes at the same time in wider samples. Nevertheless, statistic corrections must be stricter in these types of studies, because increasing the number of performed tests also increases the risk of suffering false positive results.

Animal models, mainly mice and macaque monkeys

The use of animal models to recreate pathology, or experimentation conditions, is very important due to human limitations. Mice are a good model because they show characteristics of temperament similar to humans, such as Novelty Seeking or Harm Avoidance. It has been observed that knockout mice for *stathmin* gene are immune to fear [45]. Nevertheless, the best models to study temperament are primates, due to their proximity to humans. Suomi et al [46] studied a newborn sample of *Macaca mulatta*, measuring different temperamental variables. Some of these variables were associated to *5-HTTLPR* polymorphism. Monkeys with *s* allele showed less reactivity in response to stimuli in a stressful environment. Other studies have also supported the role of 5-HTTLPR in reactivity and anxiety in this species [47].

Gene-environment studies

We have already discussed an interaction between *5-HTT* and *DRD4* and temperament, at least during the first years of child life. Besides the interaction between genes, there would be many interactions between environment and genes. In adults, the presence of *5-HTTLPR- s* allele has been associated with higher vulnerability to depression in response to vital events [49]. An association between the Val158 variant of the *COMT* gene and higher probability of suffering schizophrenia when consuming cannabis has been found [49]. In children the number of environmental factors is smaller and easier to control than in adults, so this type of study is more likely to be successful.

CONCLUSIONS

Adoption and twin studies indicated that heritability of temperament reach values between moderate and high. Molecular genetic studies have identified several genes with a likely role in temperament, such as *5-HTT* and *DRD4*. The involvement of *MAOA* is also well-known in some personality and behaviour disorders. All these genes have been suggested as candidates for future studies which could reveal new genetic polymorphisms modulating temperament.

In order to avoid false positive results and low replicability of genetic studies, it is necessary to unify criteria when defining temperament, as well as when using the different scales of measurement. In addition, it is also crucial to increase the power of the studies, using higher samples in each study. On other hand, model animals and gene-environment studies would open new ways to deal with the study of temperament. Longitudinal projects starting at birth in large samples of children (collecting genetic and environmental data and focusing in the analysis of different development stages) could be the best choice to improve the lack of knowledge in this area.

BIBLIOGRAFÍA

1. McClelland DC. Is personality consistent? In Rabin **INICIAL?**, ed. Further exploration in personality. New York: John Wiley; 1981. **págs??**
2. Sanjuán J, Moltó MD. La personalidad: genética y evolución. In Roca **INICIAL?,** ed. Trastornos de personalidad. Barcelona: STM; 2003. **páginas??**
3. Caspi A, Henry B, McGee RO, Moffitt TE, Silva PA. Temperamental origins of child and adolescent behavior problems: from age three to age fifteen. Child Dev 1995; 66: 55-68.
4. Rende RD. Longitudinal relations between temperament traits and behavioral syndromes in middle childhood. J Am Acad Child Adolesc Psychiatry 1993; 32: 287-90.
5. Brandes M, Bienvenu OJ. Personality and anxiety disorders. Curr Psychiatry Rep 2006; 8: 263-9.
6. Mervielde I, **De CB, De FF, Van LK??**. Temperament, personality, and developmental psychopathology as childhood antecedents of personality disorders. J Personal Disord 2005; 19: 171-201.
7. Savitz JB, Ramesar RS. Personality: is it a viable endophenotype for genetic studies of bipolar affective disorder? Bipolar Disord 2006; 8: 322-37.
8. Snidman KJ. The tapestries of temperament. In Snidman KJ, ed. The long shadow of temperament. **CIUDAD:??** Harvard University Press; 2004. p. 34-64.
9. Pesonen AK, Raikkonen K, Kajantie E, Heinonen K, Strandberg TE, Jarvenpaa AL. Fetal programming of temperamental negative affectivity among children born healthy at term. Dev Psychobiol 2006; 48: 633-43.
10. Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993; 50: 975-90.
11. Cloninger CR. A systematic method for clinical description and classification of personality variance: a proposal. Arch Gen Psychiatry. 1987; 44: 573-88.
12. Jang KL, Vernon PA, Livesley WJ. Behavioural-genetic perspectives on personality function. Can J Psychiatry 2001; 46: 234-44.
13. Savitz JB, Ramesar RS. Genetic variants implicated in personality: a review of the more promising candidates. Am J Med Genet B Neuropsychiatr Genet 2004; 131: 20-32.
14. Buss AH, Plomin R. A temperament theory of personality development. New York: John Wiley; 1975. p. **páginas??**
15. Rowe DC, Plomin R. Temperament in early childhood. J Pers Assess 1977; 41: 150-6.
16. Bayley N. Bayley scales of mental development. New York: Psychological Corporation; 1969. **páginas??**
17. Brazelton TB, Nugent JK. The Neonatal Behavioral Assessment Scale. Cambridge: MacKeith Press; 1995. **páginas??**
18. Saudino KJ. Behavioral genetics and child temperament. J Dev Behav Pediatr 2005; 26: 214-23.
19. Chess S, Thomas A. Temperamental individuality from childhood to adolescence. J Am Acad Child Psychiatry 1977; 16: 218-26.
20. Plomin R, Emde RN, Braungart JM, Campos J, Corley R, Fulker DW, et al. Genetic change and continuity from fourteen to twenty months: the MacArthur Longitudinal Twin Study. Child Dev 1993; 64: 1354-76.
21. Cyphers LH, Phillips K, Fulker DW, Mrazek DA. Twin temperament during the transition from infancy to early childhood. J Am Acad Child Adolesc Psychiatry 1990; 29: 392-7.
22. Braungart JM, **PR??**, DeFries JD, Fulker DW. Genetic influence on tester-rated infant temperament as assessed by Bayley's Infant Behavior Record: nonadoptive and adoptive siblings and twins. Dev Psychol 1992; 28: 40-7.
23. Plomin R, Corley R, Caspi A, Fulker DW, DeFries JD. Adoption results for self-reported personality: evidence for nonadditive genetic effects? J Pers Soc Psychol 1998; 75: 211-8.
24. Braungart JM, Fulker DW, Plomin R. Genetic influence on the home environment during infancy: a sibling adoption study of the HOME. Dev Psychol 1992; 28: 1048-55.
25. Matheny AP, Jr. *Bayley's Infant Behavior Record*: behavioral components and twin analyses. Child Dev 1980; 51: 1157-67.
26. 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.
27. Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, et al. Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. Nat Genet 1996; 12: 78-80.
28. Hamer DH, Greenberg BD, Sabol SZ, Murphy DL. Role of the serotonin transporter gene in temperament and character. J Personal Disord 1999; 13: 312-27.
29. Herbst JH, Zonderman AB, McCrae RR, Costa PT Jr. Do the dimensions of the temperament and character inventory map a single genetic architecture? Evidence from molecular genetics and factor analysis. Am J Psychiatry 2000; 157: 1285-90.
30. Bengel D, Heils A, Petri S, Seemann M, Glatz K, Andrews A, et al. Gene structure and 5'-flanking regulatory region of the murine serotonin transporter. Brain Res Mol Brain Res 1997; 44: 286-92.
31. Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O, et al. Multiple dopamine D4 receptor variants in the human population. Nature 1992; 358: 149-52.
32. Lynn DE, Lubke G, Yang M, McCracken JT, McGough JJ, Ishii J, et al. Temperament and character profiles and the dopamine D4 receptor gene in ADHD. Am J Psychiatry 2005; 162: 906-13.
33. Ebstein RP, Levine J, Geller V, Auerbach J, Gritsenko I, Belmaker RH. Dopamine D4 receptor and serotonin transporter promoter in the determination of neonatal temperament. Mol Psychiatry 1998; 3: 238-46.
34. Auerbach J, Geller V, Lezer S, Shinwell E, Belmaker RH, Levine J, et al. Dopamine D4 receptor (D4DR) and serotonin transporter promoter (5-HTTLPR) polymorphisms in the determination of temperament in 2-month-old infants. Mol Psychiatry 1999; 4: 369-73.
35. Korner AF, Zeanah CH, Linden J, Berkowitz RI, Kraemer HC, Agras WS. The relation between neonatal and later activity and temperament. Child Dev 1985; 56: 38-42.
36. Lakatos K, Nemoda Z, Birkas E, Ronai Z, Kovacs E, Ney K, et al. Association of D4 dopamine receptor gene and serotonin transporter promoter polymorphisms with infants' response to novelty. Mol Psychiatry 2003; 8: 90-7.
37. Beitchman JH, Baldassarra L, Mik H, **De L, V??,** King N, Bender D et al. Serotonin transporter polymorphisms and persistent, pervasive childhood aggression. Am J Psychiatry 2006; 163: 1103-5.
38. Lee HJ, Lee HS, Kim YK, Kim L, Lee MS, Jung IK, et al. D2 and D4 dopamine receptor gene polymorphisms and personality traits in a young Korean population. Am J Med Genet B Neuropsychiatr Genet 2003; 121: 44-9.
39. Johnson EG. Association study between dopamine D3 receptor gene variant and personality traits. Am J Med Genet 2003; **VOL., PÁGS??**
40. VanNess SH, Owens MJ, Kilts CD. The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. BMC Genet 2005; 6: 55.
41. Kusumi I, Suzuki K, Sasaki Y, Kameda K, Sasaki T, Koyama T. Serotonin 5-HT(2A) receptor gene polymorphism, 5-HT(2A) receptor function and personality traits in healthy subjects: a negative study. J Affect Disord 2002; 68: 235-41.
42. Ebstein RP, Segman R, Benjamin J, Osher Y, Nemanov L, Belmaker RH. 5-HT2C (HTR2C) serotonin receptor gene polymorphism associated with the human personality trait of reward dependence: interaction with dopamine D4 receptor (D4DR) and dopamine D3 receptor (D3DR) polymorphisms. Am J Med Genet 1997; 74: 65-72.
43. De Boer L, Roder I, Wit JM. Psychosocial, cognitive, and motor functioning in patients with suspected Sotos syndrome: a comparison between patients with and without NSD1 gene alterations. Dev Med Child Neurol 2006; 48: 582-8.
44. Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW, et al. MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and a meta-analysis. Mol Psychiatry 2006; 11: 903-13.
45. Shumyatsky GP, Malleret G, Shin RM, Takizawa S, Tully K, Tsvetkov E, et al. Stathmin, a gene enriched in the amygdala, controls both learned and innate fear. Cell 2005; 123: 697-709.
46. Champoux M, Bennett A, Shannon C, Higley JD, Lesch KP, Suomi SJ. Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates. Mol Psychiatry 2002; 7: 1058-63.
47. Bennett AJ, Lesch KP, Heils A, Long JC, Lorenz JG, Shoaf SE, et al. Early experience and serotonin transporter gene variation interact to influence primate CNS function. Mol Psychiatry 2002; 7: 118-22.
48. 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.
49. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biol Psychiatry 2005; 57: 1117-27.

GENÉTICA DEL TEMPERAMENTO EN NIÑOS

Resumen. Introducción. *A pesar de que inicialmente dio resultados esperanzadores, el estudio de las bases genéticas de la personalidad no ha logrado unos resultados satisfactorios. Las razones básicas han sido la cuestionable validez biológica de las dimensiones de la personalidad y la importante contribución del ambiente. Una alternativa ha sido recurrir al estudio del temperamento en niños (lactantes y preescolares) en los que la variabilidad del comportamiento individual está menos modulada por factores ambientales.* Desarrollo. *En primer lugar se presentan los estudios de gemelos y de adopción, que determinan el grado de heredabilidad del temperamento en niños, y se comparan con los estudios de personalidad en adultos. Seguidamente se pasa a comentar los estudios de asociación realizados con el fin de identificar los genes que intervienen en las bases moleculares del temperamento en niños, principalmente los estudios relacionados con el gen transportador de serotonina* (5-HTT)*, el gen receptor* (DRD4) *y el gen* monoamino oxidasa A (MAOA)*, relacionados con dimensiones específicas o trastornos de la personalidad. Por último, se analizan las futuras direcciones hacia las que se dirige este campo de investigación.* Conclusión. *La investigación del temperamento en niños presenta una heredabilidad más elevada que la personalidad en adultos. Los polimorfismos de los genes* 5-HTT *y* DRD4 *contribuyen a explicar parte de la variabilidad observada en el comportamiento individual. Aun así, la falta de replicabilidad en los estudios actuales hace necesarios nuevos enfoques, y son particularmente relevantes los estudios longitudinales que introduzcan la investigación de las interacciones geneticoambientales. [REV NEUROL 2007; 45:]*

Palabras clave. 5-HTT. DRD4. *Estudios de asociación. Genética.* MAOA. *Niños. Personalidad. Temperamento.*