World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

*World J Psychiatr* 2021 September 19; 11(9): 530-542

DOI: 10.5498/wjp.v11.i9.530

ISSN 2220-3206 (online)

*MINIREVIEWS*

# Genetics of adult attachment: An updated review of the literature

Leire Erkoreka, Mercedes Zumarraga, Aurora Arrue, M Isabel Zamalloa, Ainara Arnaiz, Olga Olivas, Teresa Moreno-Calle, Estela Saez, Jon Garcia, Elena Marin, Noemi Varela, Ana Gonzalez-Pinto, Nieves Basterreche

**ORCID number:** Leire Erkoreka 0000-0002-9104-0694; Mercedes Zumarraga 0000-0003-0073-8198; Aurora Arrue 0000-0002-9173-6229; M Isabel Zamalloa 0000-0001-8090-0081; Ainara Arnaiz 0000-0002-4330-8529; Olga Olivas 0000-0002-2618-1204; Teresa Moreno-Calle 0000-0002-5970-7524; Estela Saez 0000-0001-7039-0065; Jon Garcia 0000-0003-2529-3308; Elena Marin 0000-0002-3712-2883; Noemi Varela 0000-0001-6019-5442; Ana Gonzalez-Pinto 0000-0002-2568-5179; Nieves Basterreche 0000-0003-2234-6929.

**Author contributions:** Erkoreka L, Zumarraga M, Arrue A, Zamalloa MI, Arnaiz A, Olivas O, Moreno-Calle T, Saez E, Garcia J, Marin E, Varela N and Basterreche N contributed to the literature search and article review; Erkoreka L, Zumarraga M, Arrue A and Basterreche N wrote the draft; Gonzalez-Pinto A contributed to the revision; All authors revised and approved the final manuscript.

**Conflict-of-interest statement:** The authors have no conflicts of interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0)

**Leire Erkoreka, Teresa Moreno-Calle, Estela Saez,** Department of Psychiatry, Galdakao-Usansolo Hospital, Osakidetza Basque Health Service, Galdakao 48960, Spain

**Leire Erkoreka, Jon Garcia,** Department of Neurosciences, University of the Basque Country UPV/EHU, Leioa 48940, Spain

**Leire Erkoreka, Mercedes Zumarraga, Aurora Arrue, M Isabel Zamalloa, Ainara Arnaiz, Olga Olivas, Teresa Moreno-Calle, Jon Garcia, Elena Marin, Noemi Varela,** Grupo Red de Salud Mental, Biocruces Bizkaia Health Research Institute, Barakaldo 48903, Spain

**Mercedes Zumarraga, Aurora Arrue, M Isabel Zamalloa,** Department of Neurochemical Research, Bizkaia Mental Health Network, Osakidetza Basque Health Service, Barakaldo 48903, Spain

**Ainara Arnaiz,** Erandio Mental Health Center, Bizkaia Mental Health Network, Osakidetza Basque Health Service, Erandio 48950, Spain

**Olga Olivas,** Zaldibar Hospital, Bizkaia Mental Health Network, Osakidetza Basque Health Service, Zaldibar 48250, Spain

**Jon Garcia, Noemi Varela, Nieves Basterreche,** Zamudio Hospital, Bizkaia Mental Health Network, Osakidetza Basque Health Service, Zamudio 48170, Spain

**Elena Marin,** Bermeo Hospital, Bizkaia Mental Health Network, Osakidetza Basque Health Service, Bermeo 48370, Spain

**Ana Gonzalez-Pinto,** Department of Psychiatry, BioAraba Research Institute, Araba University Hospital, University of the Basque Country (UPV/EHU), CIBERSAM, Vitoria-Gasteiz 01004, Spain

**Nieves Basterreche,** Grupo de investigación integradora en Salud Mental, Biocruces Bizkaia Health Research Institute, Barakaldo 48903, Spain

**Corresponding author:** Leire Erkoreka, MD, PhD, Associate Chief Physician, Department of Psychiatry, Galdakao-Usansolo Hospital, Osakidetza Basque Health Service, Labeaga Auzoa 46A, Galdakao 48960, Spain. leire.erkorekagonzalez@osakidetza.eus

## Abstract

Attachment style, which has been theorized to be rooted in childhood bonding experiences, influences adult cognitive, emotional and interpersonal functioning. Despite its relationship with early experiences, research indicates that the continuity of attachment style across childhood and adulthood is only partial,

license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Specialty type:** Psychiatry

**Country/Territory of origin:** Spain

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

**Received:** February 25, 2021
**Peer-review started:** February 25, 2021
**First decision:** April 21, 2021
**Revised:** May 4, 2021
**Accepted:** July 29, 2021
**Article in press:** July 29, 2021
**Published online:** September 19, 2021

**P-Reviewer:** Arumugam VA, Miwa T, Zhang XQ
**S-Editor:** Gao CC
**L-Editor:** Filipodia
**P-Editor:** Guo X

being a malleable tendency that is shaped throughout development, with an increasing influence of genetics, as it occurs in other cognitive and behavioral phenotypes. Genetic research indicates that up to 45% of the variability in anxious and 39% in avoidant adult attachment style could be explained by genetic causes, but the precise mechanisms remain unclear. A narrative review is conducted analyzing the existing literature regarding the implication of candidate genes related to oxytocin, dopaminergic pathways, serotonergic pathways and brain-derived neurotrophic factor in adult attachment, with both vulnerability and differential susceptibility approaches, yielding mixed results. We highlight the lack of genome-wide studies and the scarcity of epigenetic investigation. Based on the existing data, we conclude that the genetics of adult attachment is an area that requires further research to clarify its etiological role and that it should be preferably approached as an interaction between nature and nurture.

**Key Words:** Genetics; Adult attachment; Oxytocin; Dopamine; Serotonin; Brain-derived neurotrophic factor; Methylation

**©The Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** Attachment style influences adult cognitive, emotional and interpersonal functioning. Despite its relationship with early experiences, it is a malleable tendency that is shaped throughout development. Genetic research indicates that up to 45% of the variability in anxious and 39% in avoidant adult attachment style could be explained by genetic causes. A narrative review is conducted analyzing the existing literature regarding the implication of candidate genes, with vulnerability and differential susceptibility approaches. We highlight the lack of genome-wide studies and scarcity of epigenetic investigation, concluding that further research is needed to clarify the etiological role of genetics on adult attachment.

**Citation:** Erkoreka L, Zumarraga M, Arrue A, Zamalloa MI, Arnaiz A, Olivas O, Moreno-Calle T, Saez E, Garcia J, Marin E, Varela N, Gonzalez-Pinto A, Basterreche N. Genetics of adult attachment: An updated review of the literature. *World J Psychiatr* 2021; 11(9): 530-542
**URL:** https://www.wjgnet.com/2220-3206/full/v11/i9/530.htm
**DOI:** https://dx.doi.org/10.5498/wjp.v11.i9.530

## INTRODUCTION

Attachment has been defined as the tendency of human beings to create strong affective bonds towards specific figures and explains the various forms of emotional stress and personality pathology, including anxiety, anger, depression and emotional detachment, that result from unwanted separation or loss of such figures[1]. During childhood, the relationship with the parent is the primary attachment, and this will be gradually replaced, during adolescence and adulthood, by social and romantic relationships.

Broadly speaking, the type of attachment can be defined as secure or insecure. Different proposals describe distinct types of insecure attachment, as we will detail below, although the most widely used is the two-dimensional one that distinguishes anxious and avoidant attachment styles. Secure attachment is seen as an internal resource that allows for the management of negative emotions and the recovery of calm, as well as a source of resilience. In contrast, an insecure attachment style facilitates the development of psychological distress and eventual psychopathology [2]. It has been shown that the attachment style plays a determining role in cognitive, emotional and social-interactional aspects of the individual.

## ATTACHMENT STYLES

The concept of attachment style was first proposed by Ainsworth in the 1970s to

describe children's response patterns to separation from their mothers during the Strange Situation Procedure, designed to assess attachment pattern[3]. Children were described as secure if they showed separation distress and sought contact and calmed down with the mother after the reunion. On the other hand, children were classified as insecure-avoidant if they showed little separation distress and avoided contact with their mother after the reunion. Finally, insecure-ambivalent/resistant children were those who showed extreme distress before separation and ambivalent behaviors after the meeting with the mother. It has been proposed that deactivation of the attachment system occurs in avoidant children and hyperactivation in ambivalent/resistant children. Later, Main and Solomon[4] added the disorganized attachment style to describe those children who did not present coherent attachment strategies, oscillating between different types or presenting bizarre behavior after the reunion.

Beginning in the 1980s, several researchers developed new measures to assess attachment style in order to extend the study to adolescents and adults. Maintaining a developmental perspective, George *et al*[5] developed the Adult Attachment Interview (AAI), which assessed the mental representations of attachment (or states of mind in relation to attachment) towards the parents in relation to childhood. Through this interview, the attachment style was classified as secure, dismissing, preoccupied or unresolved/disorganized[5].

In the same period, Hazan and Shaver[6] developed a self-administered questionnaire to assess attachment in adult relationships, and based on Ainsworth's styles, the individual was classified as secure, avoidant or anxious/ambivalent[6]. With a similar focus, Bartholomew and Horowitz[7] developed another proposal, in which attachment was also assessed by means of a self-administered questionnaire and classified as secure, dismissive, preoccupied or fearful. It gradually became evident that adult attachment could be assessed along two main dimensions: Anxiety and avoidance[8]. Anxiety explores concern regarding the availability and responsiveness of the other, and avoidance, on the other hand, evaluates interindividual differences regarding the degree of comfort with closeness and interdependence. It has been proposed that low scores on both anxiety and avoidance are suggestive of secure attachment; high scores on anxiety alone would indicate an anxious type of insecure attachment; high scores on avoidance alone would indicate an avoidant type of insecure attachment; and high scores on both dimensions would be suggestive of disorganized attachment, although a solely dimensional treatment of the two variables is recommended[2].

## STABILITY AND CHANGE OF THE ATTACHMENT SYSTEM

Adult attachment research, therefore, has been conducted using the two aforementioned models. The first is based on the AAI, a semi-structured interview that explores the adult's current state of mind and the coherence of discourse in relation to childhood attachment experiences, and the second is based on the evaluation through self-administered questionnaires of beliefs and experiences related to attachment in the adult's current relationships with significant others. Nevertheless, although both maintain the same theoretical background, divergences have been found in the results obtained between the two models, with correlations interpreted as trivial to small[9]. These results suggest that there is no significant equivalence between attachment measured with the AAI, more focused on childhood experiences, and that assessed with self-administered questionnaires in relation to current significant figures.

A lack of continuity has also been observed even between childhood attachment and that assessed in adults using the AAI or equivalents, despite the fact that both assess the quality and style of the relationship with the parents during childhood. A meta-analysis concluded that the overall stability in the type of attachment assessed by the Strange Situation Procedure (or equivalents) in childhood and by the AAI (or equivalents) in adulthood was 0.39, which is interpreted as medium-sized stability. However, there was no significant stability for intervals longer than 15 years. Interestingly, and in relation to subgroups with psychosocial risks, it was observed that securely attached children that belonged to these groups were less likely to maintain attachment security, whereas insecurely attached children were most likely to maintain insecurity[10].

These results suggest the existence of other variables that would act throughout development and that would intervene in the shaping of adult attachment. In this sense, it has been described that in addition to the relationship with caregivers in childhood, emerging social competence (the socialization skills of children assessed by

their teachers at school) and the quality of the relationship with best friends in childhood-adolescence independently and significantly influence adult attachment style[11].

Working models of attachment formed in infancy are sensorimotor, procedural and nonlinguistic in nature, reflecting interactions between the infant and caregiver that occurred prior to the emergence of linguistic and introspective abilities. Thus, different theorists have contributed to the development of a "prototype" theory that posits the coexistence of current working models and early prototypical models. Prototypical working models formed during early life would continue to exist and exert a shaping effect on attachment patterns throughout life, both by attempting to match new experiences to pre-existing models and by reinforcing them through behaviors that elicit reactions consistent with the individual's expectations. In addition, current ones would be revised and updated as relevant attachment experiences arise that differ from, or challenge, previous experiences and knowledge (such as the loss of an attachment figure or infidelities), thus enabling and explaining variations in attachment style across the lifespan[2]. In the same line, other authors also describe that children's attachment patterns are malleable and shaped by multiple experiences in the transition to adulthood, pointing out that socialization and selection effects have a differential influence according to the life stage[12].

## ADULT ATTACHMENT AND PERSONALITY

The relationship between attachment style and personality is also an aspect to be considered in this area of investigation. Although attachment research tends not to emphasize the temperamental contribution to attachment styles, Bowlby[13] himself suggested that there may be preexisting temperamental differences in children and that attachment experiences would modulate, interact with or overcome these differences. In this line, several authors have described a certain degree of overlap in the heritability of personality features and attachment styles in studies carried out using self-administered questionnaires to explore adult attachment[14-16]. It has been reported that 63% of the association between attachment anxiety and personality dimensions was attributable to common genetic effects[14]. Other authors described that genetic influence on neuroticism contributed to 35% of the variance in anxiety and 11% in avoidance, whereas genetic influence on extraversion contributed to 6% of the variance in avoidance[15].

In a study conducted by our group with a general population sample, we found that a functional polymorphism in the catechol-o-methyltransferase (COMT) gene had a common influence on avoidant attachment and inhibitedness personality dimension. This was not due to a poor discriminative capacity of the instruments, since independent associations were observed, for example, between a polymorphism in the serotonin transporter (5HTT) gene and both variables[16].

In this regard, it has been proposed that temperamental characteristics, which are strongly influenced by genetics, would influence internal working models of attachment in complex ways, including person-environment interaction and gene-environment interaction[15]. In addition to the genetic conditioning that may exist, and that will constitute the temperamental basis by which the individual tends to experience certain affects in his or her experience of the other, starting from primary object relations, there is a continuous and close interaction between personality and attachment style throughout development. It will determine the social choices and the way in which the individual perceives relationships throughout life. The greater capacity of the adult to make these social decisions, determined in part by temperamental aspects, could explain to some degree the discrepancies observed between samples of children and adults in genetic research of attachment, which are detailed below.

## GENETICS OF ADULT ATTACHMENT

### *Methods*

A literature search was performed to identify studies on genetics of adult attachment. Articles published until December 28, 2020 were retrieved from the PubMed database using broad search terms in order to identify as many potentially eligible studies as possible: [(attachment OR "adult attachment") AND (genetic* OR dopamine* OR

COMT OR serotonin* OR oxytocin* OR brain-derived OR BDNF)]. An age filter was added: "Adults: 19+ years". The reference lists of the selected studies and reviews were also checked to identify additional relevant articles using a snowballing approach. Studies were included if: (1) They investigated the influence of genetics/epigenetics on adult attachment using any approach (twin-studies, genome-wide studies or candidate gene studies); (2) They used standard measures of adult attachment (AAI or self-administered questionnaires); (3) They were systematic reviews, meta-analyses, narrative reviews or original research studies; and (4) They were written in English or Spanish.

This is not a systematic review but a narrative one; it summarizes the findings described in the selected reports and, in this way, provides an overview on the subject.

### *Heritability of attachment: Twin-studies*

In twin-studies of children, the combination of shared and nonshared environmental variables seems to explain most of the variability in attachment style, with no significant weight of genetics observed[17-19]. Shared environmental factors have been described as the environmental influences responsible for resemblance between family members, and nonshared environmental factors as those influences that contribute to differences between family members[20].

In contrast to what has been observed in children, independent twin studies in adolescents and adults describe that attachment is mainly conditioned by genetic and nonshared environmental factors[14,15,21-24]. The only study of adolescent twins to date was conducted using the Child Attachment Interview, a childhood adaptation of the AAI that explores coherence of discourse and childhood attachment experiences in relation to parents. They found that genetic effects accounted for 35% of the variance in attachment security and that the remaining 65% was estimated to be due to the nonshared environment[22].

Most of the twin-studies in adults have been conducted using self-reported questionnaires, but the results are generally similar to those obtained in the adolescent study. The heritability of anxious attachment has been described to be between 37% and 40% in two different studies, the rest being explained by nonshared environmental factors[14,21]. These two groups did not observe avoidant attachment to be explained by genetics. In other studies, however, the heritability of anxious attachment was replicated, and genetic influence was also described for the avoidant style. Additive genetic effects were described to account for 45% of the variability in anxiety and 39% in avoidance in the Michigan State University Twin Study of Behavioral Adjustment[15]. These figures were similar to those obtained in another study, where genetic effects accounted for 45% of individual differences in anxiety and 36% in avoidant attachment[23]. The only report exploring attachment with the AAI in adult twins described that attachment styles were determined by genetics and shared environment[24]; nonetheless, it was a pilot study with a limited sample size.

The differences in heritability observed between studies carried out with samples of children and adult samples are consistent with the lack of stability in attachment style described in longitudinal studies, as we have previously mentioned. They could be due to the way the exploration of attachment is operationalized depending on age; whereas in children it is based on differences in observed attachment behaviors, in adults it is focused on the way individuals think about their attachment relations, in relation to their parents (with the AAI) or in relation to their current close relationships (with self-administered questionnaires).

In addition, age-related increases in genetic influences on various cognitive, behavioral and psychiatric phenotypes have been well-documented, some authors suggesting that shared environmental effects may be relatively restricted to infancy and, when present, may not be stable beyond childhood[25]. The influence of the environment would decrease with age, as the children undergo a variety of influences outside the family, and are more able to shape their own environments[26]. In this line, an increasing influence of genetics has also been observed in relation to affiliation with peers in a relatively short range of years, concretely in the transition from adolescence to adulthood (between the ages of 15 and 21)[27].

### *Genome-wide association studies*

The first genome-wide association study (GWAS) on attachment patterns was conducted in children, providing evidence of novel genes (HDAC1, ZNF675, BSCD1) associated with attachment disorganization[28], but these findings have not been replicated. A subsequent epigenome-wide association study reported that infant attachment was also significantly associated with a principal component that

accounted for 11.9% of the variation in genome-wide DNA methylation[29]. Methylation is associated with lower levels of transcription of a gene when it occurs in the promoter region. The observed effects were most apparent when comparing children with a secure *vs* a disorganized attachment style, and most pronounced in females, providing preliminary evidence for a molecular signature of infant attachment. The complexity of child attachment assessment makes it difficult to conduct studies that involve the analysis of the whole genome and thus require large samples, being the samples of both studies of limited size (samples sizes of 657 and 226, respectively) compared to others of this type. To date, no GWAS on adult attachment have been published.

### *Candidate gene studies*

The bulk of research in adult attachment genetics has been conducted based on a candidate gene approach and has mainly involved polymorphisms in the oxytocin receptor (OXTR) gene and in those involved in dopaminergic and serotonergic pathways, although more recent work has also studied brain-derived neurotrophic factor (BDNF). Candidate gene studies have been conducted reporting either direct associations or gene-by-environment interactions (known respectively as vulnerability and plasticity genes, see Belsky *et al*[30]). We will describe the main findings using both approaches. The findings are summarized in Table 1.

**OXTR:** Oxytocin (OXT) is a neuropeptide synthesized in the hypothalamus whose known role in the periphery is as an initiator of childbirth and lactation. It also has a central role in social and emotional behavior, insofar as it participates in the formation of emotional bonds across the lifespan[31]. In fact, OXTR are concentrated in brain regions involved in social behavior, including the olfactory processing regions, limbic brain structures, hippocampus, hypothalamus and brainstem[32].

Plasma concentrations of OXT and genetic polymorphisms that involve OTX action, mainly the OXTR gene, have been studied in relation to different aspects of socialization in animals and humans, including attachment. OXTR gene is located on the short arm of chromosome 3 (3p25) and has three introns and four exons. Several dozens of single-nucleotide polymorphisms (SNP) have been identified in the OXTR gene region[33]; among them, rs53576 and rs2254298, located in intron 3, are the most extensively studied in relation to social behavior. In both cases, they consist of mutations in which a guanine (G) base is replaced by an adenine (A) base.

The functionality of these polymorphisms remains unclear[34]. They do not change the amino acid sequence of the encoded protein, and thus it has been proposed that they should exert their effects through variations in brain structure and function[35]. The A allele of rs53576 has been associated with morphometric and functional alterations in hypothalamus and amygdala that predicted lower levels of reward dependence[36]. The rs2254298 OXTR A allele has been associated with larger amygdala volume in different populations[37,38]. These studies provide evidence of a possible convergent impact of OXTR polymorphisms on this key limbic structure.

In relation to adult attachment, an association of the GG genotype of rs53576 with greater insecurity according to self-administered questionnaires has been described [39], and conversely, that this genotype is associated with lower anxiety and avoidance [40]. With regard to rs2254298, the GG genotype has been associated with greater avoidance[39] and lower anxiety[41], the latter in women. Other authors, however, have not found significant associations between these two polymorphisms and attachment styles[11,42,43].

Further, it has been described that rs53576 acts as a moderator in the continuity of secure attachment from childhood to adulthood, so that in those individuals with the GG genotype, infant attachment security predicted romantic attachment security in adulthood[44].

Finally, when we study the interaction of the OXTR gene genotypes with environmental variables, a role in the intergenerational transmission of attachment, in interaction with childrearing style, has been reported[45], whereas other authors have not found any interaction with parental sensitivity[11]. Recent epigenetic studies coincide in describing that the higher the methylation in the promoter region of the OXTR gene, the higher the avoidant attachment score[46,47]. These studies have been conducted on saliva and peripheral blood samples, respectively.

**Dopaminergic system:** Regarding the dopaminergic pathway, the genes of the dopaminergic receptors D2 (DRD2) and D4 (DRD4) and of the COMT have been mainly studied.

**Table 1 Summary of candidate gene studies on adult attachment**

| Gene | Marker | Ref. | Adult attachment measure | Result |
|---|---|---|---|---|
| *OXTR* | rs53576 | Costa *et al*[39], 2009 | ASQ | GG greater insecurity |
| | | Monin *et al*[39], 2019 | ECR | GG lower anxiety and avoidance |
| | | Raby *et al*[44], 2013 | CRI | GG predicts continuity of attachment security |
| | | Fraley *et al*[11], 2013 | RSQ | No significant associations or interactions with maternal sensitivity |
| | | Gillath *et al*[42], 2008 | ECR | No significant associations |
| | | Gong *et al*[43], 2020 | RAAS | No significant associations |
| | rs2254298 | Costa *et al*[39], 2009 | ASQ | GG higher avoidance |
| | | Chen and Johnson[41], 2012 | ECR | GG lower anxiety in females |
| | | Fraley *et al*[11], 2013 | ECR | No significant associations or interactions with maternal sensitivity |
| | | Gong *et al*[43], 2020 | RAAS | No significant associations |
| | Methylation promoter region | Ebner *et al*[46], 2019 | ECR | Higher methylation associated with higher avoidance |
| | | Ein-Dor *et al*[47], 2018 | AAS | Higher methylation associated with higher avoidance |
| *DRD2* | rs1800497 | Gong *et al*[43], 2020 | RAAS | A1 homozygotes higher anxiety than A2 carriers |
| | | Fraley *et al*[11], 2013 | ECR | No significant associations or interactions with maternal sensitivity |
| *DRD4* | VNTR | Reiner and Spangler[51], 2010 | AAI | 7R carriers greater security |
| | | Bakermans-Kranenburg *et al*[52], 2011 | AAI | 7R carriers greater susceptibility to environmental factors |
| *COMT* | rs4680 | Erkoreka *et al*[16], 2018 | ECR | ValMet heterozygotes higher avoidance than either homozygotes |
| *5HT1A* | rs6295 | Gong *et al*[43], 2020 | RAAS | G carriers less comfortable in close relationships |
| *5HT2A* | rs6313 | Gillath *et al*[42], 2008 | ECR | T homozygotes higher avoidance than C homozygotes |
| | | Salo *et al*[62], 2011 | RSQ | T homozygotes greater susceptibility to environmental factors |
| | | Fraley *et al*[11], 2013 | ECR/RSQ | C homozygotes higher anxiety (RSQ) |
| *5HTTLPR* | rs4795541 | Caspers *et al*[64], 2009 | AAI | Higher unresolved attachment |
| | | Reiner and Spangler[51], 2010 | AAI | No significant associations |
| | | Bakermans-Kranenburg *et al*[52], 2011 | AAI | No significant associations |
| | | Erkoreka *et al*[16], 2018 | ECR | No significant associations |
| | Methylation promoter region | van IJzendoorn *et al*[65], 2010 | AAI | Higher methylation in L homozygotes increased risk or unresolved loss or trauma; higher methylation in S homozygotes less unresolved loss or trauma |
| | | Jones-Mason *et al*[66], 2016 | AAI | Methylation interacts with socioeconomic status |
| *BDNF* | rs6265 | Suzuki *et al*[68], 2012 | PBI | Met carriers with low maternal care greater interpersonal sensitivity |
| | | Ibarra *et al*[69], 2014 | PBI | Met carriers greater susceptibility to childrearing style |

5HT1A: Serotonin receptor A1; 5HT2A: Serotonin receptor A2; 5HTTLPR: Serotonin transporter-linked polymorphic region; AAI: Adult Attachment

Interview; ASQ: Attachment Style Questionnaire; BDNF: Brain-derived neurotrophic factor; COMT: Catechol-o-methyltransferase; CRI: Current Relationship Interview; DRD2: Dopaminergic receptor D2; DRD4: Dopaminergic receptor D4; ECR: Experiences in Close Relationships; OXTR: Oxytocin receptor; PBI: Parental Bonding Instrument; RAAS: Revised Adult Attachment Scale; RSQ: Relationship Questionnaire.

The gene that encodes DRD2 contains a SNP (TaqIA, rs1800497) that gives rise to the A1 allele (when thymine [T] is present) or A2 allele (when cytosine [C] is present). A1 allele is associated with a reduced number of dopamine binding sites in the brain [48]. Individuals with two A1 alleles were found to score higher on attachment anxiety than those with only one, or none A1-alleles[42]. A subsequent study, however, found no relationship between this polymorphism and attachment style, either directly or in interaction with maternal sensitivity[11]. Both studies were carried out with the same self-administered questionnaire, so there was no methodological variability that could explain the differences in results.

The DRD4 gene contains a functional polymorphism consisting on a variable number of tandem repeats, in which a 48 base pair sequence exists as a 2-fold to 10-fold repeat[49]. The 7-repeat (7R) allele has been described to have a reduced ability to inhibit neuronal firing in the prefrontal cortex and thus, proposed to associate higher dopaminergic stimulation at that level[50]. There is an extensive literature on infant attachment and its relationship with this gene; however, only two studies have studied its effect on adult attachment. In both studies, the assessment of attachment style was carried out using the AAI. According to the first study, carriers of the 7R allele were significantly more likely to be securely attached, although this was only true for subjects reporting unloving caregiver recollections[51]. The authors of the second study, on their part, did not find a direct association of the polymorphism with the type of attachment. Instead, they observed that 7R allele carriers showed a heightened susceptibility to environmental influences[52], so that the carriers that reported parental problems had the highest scores for unresolved loss or trauma and the carriers without parental problems had the lowest scores. No differences according to parental problems were found among participants without the 7R allele.

COMT participates in the breakdown of dopamine and noradrenaline. Its gene contains a functional SNP (COMT Val158Met, rs4680), a substitution of G for A, which translates into an exchange of valine (Val) for methionine (Met) in the protein. MetMet homozygote individuals have four times less enzymatic activity than ValVal homozygotes, whereas heterozygotes show an intermediate level of activity. Activity associated with this polymorphism is particularly important in the prefrontal cortex, and it has been associated with numerous psychopathological phenotypes[53].

Individual heterozygous for COMT Val158Met were found to exert a more avoidant attachment pattern than homozygotes for either allele in the general population[16]. The pattern observed, in which heterozygotes scored higher than either homozygote, is called molecular heterosis. One of the explanations proposed for this fact is that on the cellular level, heterozygosity confers a broader range of genetic expressions and provides greater plasticity[54]. Although no previous or latter studies on adults have replicated this finding, they were coherent with previous research conducted in children[55].

**Serotonergic system:** Regarding the serotonergic system, both serotonin 1A (5HT1A) and 2A (5HT2A) receptor genes and the 5HTT gene have been studied.

Five-5HT1A is one of the most abundantly expressed serotonin receptors in the brain, acting at both pre- and post-synaptic neurons in several brain areas[56]. A SNP (C1019G, rs6295) in the gene has been suggested to regulate the 5HT1A receptor expression in presynaptic raphe neurons[57,58]. Compared with the C allele, the G allele is associated with higher expression in raphe neurons, leading to a decrease in firing frequency and serotonin level in synaptic cleft[57,59]. Individuals with the CG and GG genotypes have been associated with feeling less comfortable in close relationships than individuals with the CC genotype[60].

The gene that encodes 5HT2A contains a functional SNP (T102C, rs6313); the presence of T allele has been associated with reduced serotonin binding in the prefrontal cortex and, thus, with reduced serotonergic activity[61]. Individuals homozygote for T allele were found to score significantly higher on avoidant attachment than those homozygotes for C allele[42]. However, this finding was not replicated in a subsequent study, which reported that homozygotes for C allele scored higher on anxiety than T allele carriers[11]. An interaction of this polymorphism with maternal nurturance in childhood has also been observed, such that high childhood maternal nurturance predicted low avoidant attachment in the TT homozygotes but

not in carriers of C allele, whereas low maternal nurturance was associated with high avoidance in TT homozygotes but not in C allele carriers. It suggests that a gene-environmental interaction exists, with T homozygotes showing a heightened susceptibility to environmental factors[62].

The 5HTT is responsible for the recapture of serotonin from the synaptic cleft. Its gene includes a 44 base pair deletion/insertion polymorphism in the promoter region (5HTTLPR, rs4795541) and is one of the most widely studied genetic variants in psychiatric research. The long (L) allele in the promoter is associated with raised serotonin transporter messenger RNA levels, which translates into elevated transcription activity, greater transporter density and, therefore, serotonin hypofunction. The short (S) allele has the opposite effect, that is, it is associated with lower transcription activity, less transporter density and, therefore, a greater concentration of serotonin in the synapse. Further, the S allele behaves in a dominant manner [63].

An association between the S allele of 5HTTLPR and increased risk for unresolved attachment according to the AAI was described[64], although it has not been replicated. No direct effect of 5HTTLPR on attachment styles has been subsequently found, either assessed with self-report questionnaires[16] or when explored by means of the AAI[51,52].

Two studies examining methylation of the 5HTTLPR have been published so far, both of them exploring attachment styles using the AAI. Higher levels of methylation of 5HTTPR in DNA obtained from peripheral lymphoblasts were described to be associated with an increased risk of unresolved loss or trauma in homozygotes for the L allele. Higher levels of methylation in S allele homozygotes were associated with less unresolved loss or other trauma[65]. More recent research examining methylation of the 5HTTLPR gene in DNA from peripheral lymphocytes, as well as socioeconomic status (SES), concluded that lower methylation and low-SES were associated with higher unresolved loss, and higher methylation and low-SES with higher unresolved trauma. Within the unresolved category, low-SES unresolved participants had higher levels of methylation than mid/upper-SES participants, whereas SES was unrelated to methylation within the secure and organized categories[66]. Although these results require careful analysis, it appears that both gene-environment interaction and epigenetic mechanisms may play a role in the contribution of 5HTTLPR to attachment style.

**BDNF:** BDNF is one of the proteins of the neurotrophin family. It acts by promoting the survival of existing neurons, contributes to the growth and differentiation of new neurons and synapses and protects against stress-related neuronal damage. The gene encoding BDNF contains a functional SNP-like polymorphism, the BDNF Val66Met (rs6265), in which a G for A base change in the gene results in the substitution of Val for Met in the protein[67]. The presence of Met in the protein is associated with lower concentration of pro-BDNF in dendrites and secretory glands and a lower secretion of the molecule into the synaptic space.

With respect to this polymorphism, a synergistic effect has been described between being a Met carrier and low maternal care according to the Parental Bonding Instrument, leading to a greater interpersonal sensitivity[68]. In another study, Met carriers showed greater sensitivity to the childrearing style, according to the Parental Bonding Instrument, in relation to developing anxiety and somatization in adulthood [69].

## CONCLUSION

The evidence about a significant influence of genetics on adult attachment comes mainly from twin-studies, but the specific ways and mechanisms remain unclear. Research has been focused on candidate gene studies, and although some markers such as the rs53576 and rs2254298 polymorphisms in the OXTR gene seemed promising, no consistent results have been found across the studies. The same is true for the described functional polymorphisms affecting dopaminergic and serotonergic systems (in the DRD2, DRD4, COMT, 5HT1A, 5HT2A, 5HTT genes). It should be noted that the only replicated finding is the association between methylation of the promoter region of the OXTR gene and higher attachment avoidance, even using different attachment measures (in both cases, self-reports). Carrying the Met allele in the BDNF rs6265 polymorphism also seems to confer certain vulnerability to environmental factors related to childrearing, although the studies published so far have been conducted with different methodology, making it difficult to compare the results.

Admittedly, the scarcity of data, the methodological differences in relation to the exploration of the adult attachment (AAI *vs* self-administered questionnaires) and the doubts raised about the comparability of data obtained in children (more abundant) and adults make it difficult to draw conclusions regarding the specific contribution of genetics to adult attachment. Different authors propose that the weight of genetics and environment on attachment styles differs in childhood and adulthood, so that during childhood the shared environment would be the main contributor to attachment style, whereas the biological-temperamental and the nonshared environment would acquire greater importance in adulthood[12,26,70]. These differences in the weight of genetics depending on the life stage are not unique to attachment style and have been observed in other cognitive and behavioral phenotypes as well[25,71-73].

In addition, the importance of gene-environment interaction to explain the contribution of genetics to the formation of attachment styles has also been emphasized, suggesting that research should focus more on the search for differential susceptibility or plasticity genes than on direct associations. Epigenetic research, currently in its embryonic stage in the area of attachment, has also been highlighted[26]. The studies exploring differential susceptibility, as well as epigenetic research, are precisely the ones that have yielded the most promising results to date and on which future research should probably be based.

We could therefore conclude that: (1) More research is needed to understand the precise contribution of genetics to adult attachment style; (2) Future research should take into account that the patterns observed in children and adults may differ; and (3) Additional studies should include the study of environmental variables that could affect affiliative behaviors.

## REFERENCES


1 **Bowlby J**. The Making & Breaking of Affectional Bonds. London: Tavistock, 1979
2 **Nelson JK**, Mikulincer M, Shaver PR. Attachment in Adulthood. Structure, Dynamics, and Change. *Clin Soc Work J* 2009; **37**: 179-180 [DOI: 10.1007/s10615-009-0193-5]
3 **Ainsworth M**, Blehar M, Waters E, Wall S. Patterns of attachment: Assessed in the Strange Situation and at home. Hillsdale, NJ: Erlbaum, 1978
4 **Main M**, Solomon J. Procedures for identifying infants as disorganized/disoriented during the Ainsworth Strange Situation. In: Attachment in the preschool years: Theory, research, and intervention. Chicago, IL: University of Chicago Press, 1990: 121-160
5 **George C**, Main M, Kaplan N. Adult Attachment Interview (AAI). *APA PsycNe*t 1985 [DOI: 10.1037/t02879-000]
6 **Hazan C**, Shaver P. Romantic love conceptualized as an attachment process. *J Pers Soc Psychol* 1987; **52**: 511-524 [PMID: 3572722 DOI: 10.1037//0022-3514.52.3.511]
7 **Bartholomew K**, Horowitz LM. Attachment styles among young adults: a test of a four-category model. *J Pers Soc Psychol* 1991; **61**: 226-244 [PMID: 1920064 DOI: 10.1037//0022-3514.61.2.226]
8 **Brennan KA**, Clark CL, Shaver PR. Self-report measurement of adult attachment: An integrative overview. In: Simpson JA, Rholes WS. Attachment theory and close relationships. New York, NY: Guilford Press, 1998: 46-76
9 **Roisman GI**, Holland A, Fortuna K, Fraley RC, Clausell E, Clarke A. The Adult Attachment Interview and self-reports of attachment style: an empirical rapprochement. *J Pers Soc Psychol* 2007; **92**: 678-697 [PMID: 17469952 DOI: 10.1037/0022-3514.92.4.678]
10 **Pinquart M**, Feussner C, Ahnert L. Meta-analytic evidence for stability in attachments from infancy to early adulthood. *Attach Hum Dev* 2013; **15**: 189-218 [PMID: 23210665 DOI: 10.1080/14616734.2013.746257]
11 **Fraley RC**, Roisman GI, Booth-LaForce C, Owen MT, Holland AS. Interpersonal and genetic origins of adult attachment styles: a longitudinal study from infancy to early adulthood. *J Pers Soc Psychol* 2013; **104**: 817-838 [PMID: 23397970 DOI: 10.1037/a0031435]
12 **Fraley RC**, Roisman GI. The development of adult attachment styles: four lessons. *Curr Opin Psychol* 2019; **25**: 26-30 [PMID: 29510301 DOI: 10.1016/j.copsyc.2018.02.008]
13 **Bowlby J**. Attachment and Loss. Vol 2. Separation: anxiety and anger. New York: Basic Books, 1974
14 **Crawford TN**, Livesley WJ, Jang KL, Shaver PR, Cohen P, Ganiban J. Insecure attachment and personality disorder: a twin study of adults. *Eur J Personal* 2007; **21**: 191-208 [DOI: 10.1002/per.602]
15 **Donnellan MB**, Burt SA, Levendosky AA, Klump KL. Genes, personality, and attachment in adults: a multivariate behavioral genetic analysis. *Pers Soc Psychol Bull* 2008; **34**: 3-16 [PMID: 18162654 DOI: 10.1177/0146167207309199]
16 **Erkoreka L**, Zumárraga M, Macías I, Angel Gonzalez-Torres M. The COMT Val158Met polymorphism exerts a common influence on avoidant attachment and inhibited personality, with a pattern of positive heterosis. *Psychiatry Res* 2018; **262**: 345-347 [PMID: 28807501 DOI:

10.1016/j.psychres.2017.07.053]
17 **Bokhorst CL**, Bakermans-Kranenburg MJ, Fearon RM, van IJzendoorn MH, Fonagy P, Schuengel C. The importance of shared environment in mother-infant attachment security: a behavioral genetic study. *Child Dev* 2003; **74**: 1769-1782 [PMID: 14669895 DOI: 10.1046/j.1467-8624.2003.00637.x]
18 **O'Connor TG**, Croft CM. A twin study of attachment in preschool children. *Child Dev* 2001; **72**: 1501-1511 [PMID: 11699684 DOI: 10.1111/1467-8624.00362]
19 **Roisman GI**, Fraley RC. A behavior-genetic study of parenting quality, infant attachment security, and their covariation in a nationally representative sample. *Dev Psychol* 2008; **44**: 831-839 [PMID: 18473647 DOI: 10.1037/0012-1649.44.3.831]
20 **Plomin R**, DeFries J, McClearn G, McGuffin P. Behavioral genetics. 4th ed. New York: W. H. Freeman and Company, 2012: 505
21 **Brussoni MJ**, Jang KL, Livesley WJ, Macbeth TM. Genetic and environmental influences on adult attachment styles. *Pers Relatsh* 2000; **7**: 283-289 [DOI: 10.1111/j.1475-6811.2000.tb00017.x]
22 **Fearon P**, Shmueli-Goetz Y, Viding E, Fonagy P, Plomin R. Genetic and environmental influences on adolescent attachment. *J Child Psychol Psychiatry* 2014; **55**: 1033-1041 [PMID: 24256475 DOI: 10.1111/jcpp.12171]
23 **Picardi A**, Fagnani C, Nisticò L, Stazi MA. A twin study of attachment style in young adults. *J Pers* 2011; **79**: 965-991 [PMID: 21204839 DOI: 10.1111/j.1467-6494.2010.00707.x]
24 **Torgersen AM**, Grova BK, Sommerstad R. A pilot study of attachment patterns in adult twins. *Attach Hum Dev* 2007; **9**: 127-138 [PMID: 17508313 DOI: 10.1080/14616730701349705]
25 **Plomin R**, DeFries J, Knopik V, Neiderhiser J. Behavioral Genetics. 6th ed. New York: Worth Publishers, 2013: 560
26 **Bakermans-Kranenburg MJ**, Van Ijzendoorn MH. Attachment, Parenting, and Genetics. In: Handbook of Attachment. 3rd ed. Guilford Press, 2016: 155-179
27 **Tarantino N**, Tully EC, Garcia SE, South S, Iacono WG, McGue M. Genetic and environmental influences on affiliation with deviant peers during adolescence and early adulthood. *Dev Psychol* 2014; **50**: 663-673 [PMID: 24015689 DOI: 10.1037/a0034345]
28 **Pappa I**, Szekely E, Mileva-Seitz VR, Luijk MP, Bakermans-Kranenburg MJ, van IJzendoorn MH, Tiemeier H. Beyond the usual suspects: a multidimensional genetic exploration of infant attachment disorganization and security. *Attach Hum Dev* 2015; **17**: 288-301 [PMID: 25939396 DOI: 10.1080/14616734.2015.1037316]
29 **Garg E**, Chen L, Nguyen TTT, Pokhvisneva I, Chen LM, Unternaehrer E, MacIsaac JL, McEwen LM, Mah SM, Gaudreau H, Levitan R, Moss E, Sokolowski MB, Kennedy JL, Steiner MS, Meaney MJ, Holbrook JD, Silveira PP, Karnani N, Kobor MS, O'Donnell KJ; Mavan Study Team. The early care environment and DNA methylome variation in childhood. *Dev Psychopathol* 2018; **30**: 891-903 [PMID: 30068421 DOI: 10.1017/S0954579418000627]
30 **Belsky J**, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? *Mol Psychiatry* 2009; **14**: 746-754 [PMID: 19455150 DOI: 10.1038/mp.2009.44]
31 **Hurlemann R**, Scheele D. Dissecting the Role of Oxytocin in the Formation and Loss of Social Relationships. *Biol Psychiatry* 2016; **79**: 185-193 [PMID: 26122876 DOI: 10.1016/j.biopsych.2015.05.013]
32 **Russell JA**, Brunton PJ. Oxytocin: Control of Secretion by the Brain and Central Roles. *Ref Module Neur Biob Psychol* 2017 [DOI: 10.1016/B978-0-12-809324-5.02246-X]
33 **International HapMap Consortium**, Frazer KA, Ballinger DG, Cox DR, Hinds DA, Stuve LL, Gibbs RA, Belmont JW, Boudreau A, Hardenbol P, Leal SM, Pasternak S, Wheeler DA, Willis TD, Yu F, Yang H, Zeng C, Gao Y, Hu H, Hu W, Li C, Lin W, Liu S, Pan H, Tang X, Wang J, Wang W, Yu J, Zhang B, Zhang Q, Zhao H, Zhou J, Gabriel SB, Barry R, Blumenstiel B, Camargo A, Defelice M, Faggart M, Goyette M, Gupta S, Moore J, Nguyen H, Onofrio RC, Parkin M, Roy J, Stahl E, Winchester E, Ziaugra L, Altshuler D, Shen Y, Yao Z, Huang W, Chu X, He Y, Jin L, Liu Y, Sun W, Wang H, Wang Y, Xiong X, Xu L, Waye MM, Tsui SK, Xue H, Wong JT, Galver LM, Fan JB, Gunderson K, Murray SS, Oliphant AR, Chee MS, Montpetit A, Chagnon F, Ferretti V, Leboeuf M, Olivier JF, Phillips MS, Roumy S, Sallée C, Verner A, Hudson TJ, Kwok PY, Cai D, Koboldt DC, Miller RD, Pawlikowska L, Taillon-Miller P, Xiao M, Tsui LC, Mak W, Song YQ, Tam PK, Nakamura Y, Kawaguchi T, Kitamoto T, Morizono T, Nagashima A, Ohnishi Y, Sekine A, Tanaka T, Tsunoda T, Deloukas P, Bird CP, Delgado M, Dermitzakis ET, Gwilliam R, Hunt S, Morrison J, Powell D, Stranger BE, Whittaker P, Bentley DR, Daly MJ, de Bakker PI, Barrett J, Chretien YR, Maller J, McCarroll S, Patterson N, Pe'er I, Price A, Purcell S, Richter DJ, Sabeti P, Saxena R, Schaffner SF, Sham PC, Varilly P, Stein LD, Krishnan L, Smith AV, Tello-Ruiz MK, Thorisson GA, Chakravarti A, Chen PE, Cutler DJ, Kashuk CS, Lin S, Abecasis GR, Guan W, Li Y, Munro HM, Qin ZS, Thomas DJ, McVean G, Auton A, Bottolo L, Cardin N, Eyheramendy S, Freeman C, Marchini J, Myers S, Spencer C, Stephens M, Donnelly P, Cardon LR, Clarke G, Evans DM, Morris AP, Weir BS, Mullikin JC, Sherry ST, Feolo M, Skol A, Zhang H, Matsuda I, Fukushima Y, Macer DR, Suda E, Rotimi CN, Adebamowo CA, Ajayi I, Aniagwu T, Marshall PA, Nkwodimmah C, Royal CD, Leppert MF, Dixon M, Peiffer A, Qiu R, Kent A, Kato K, Niikawa N, Adewole IF, Knoppers BM, Foster MW, Clayton EW, Watkin J, Muzny D, Nazareth L, Sodergren E, Weinstock GM, Yakub I, Birren BW, Wilson RK, Fulton LL, Rogers J, Burton J, Carter NP, Clee CM, Griffiths M, Jones MC, McLay K, Plumb RW, Ross MT, Sims SK, Willey DL, Chen Z, Han H, Kang L, Godbout M, Wallenburg JC, L'Archevêque P, Bellemare G, Saeki K, An D, Fu H, Li Q, Wang Z, Wang R, Holden AL, Brooks LD, McEwen JE, Guyer MS, Wang VO, Peterson JL, Shi M, Spiegel J, Sung LM,

Zacharia LF, Collins FS, Kennedy K, Jamieson R, Stewart J. A second generation human haplotype map of over 3.1 million SNPs. *Nature* 2007; **449**: 851-861 [PMID: 17943122 DOI: 10.1038/nature06258]

34 **GeneCards**. GeneCards-Human Gene Database. [cited 1 May 2021]. In: GeneCards [Internet]. Available from: https://www.genecards.org/

35 **Meyer-Lindenberg A**, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci* 2011; **12**: 524-538 [PMID: 21852800 DOI: 10.1038/nrn3044]

36 **Tost H**, Kolachana B, Hakimi S, Lemaitre H, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A. A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proc Natl Acad Sci U S A* 2010; **107**: 13936-13941 [PMID: 20647384 DOI: 10.1073/pnas.1003296107]

37 **Furman DJ**, Chen MC, Gotlib IH. Variant in oxytocin receptor gene is associated with amygdala volume. *Psychoneuroendocrinology* 2011; **36**: 891-897 [PMID: 21208749 DOI: 10.1016/j.psyneuen.2010.12.004]

38 **Inoue H**, Yamasue H, Tochigi M, Abe O, Liu X, Kawamura Y, Takei K, Suga M, Yamada H, Rogers MA, Aoki S, Sasaki T, Kasai K. Association between the oxytocin receptor gene and amygdalar volume in healthy adults. *Biol Psychiatry* 2010; **68**: 1066-1072 [PMID: 20832055 DOI: 10.1016/j.biopsych.2010.07.019]

39 **Costa B**, Pini S, Gabelloni P, Abelli M, Lari L, Cardini A, Muti M, Gesi C, Landi S, Galderisi S, Mucci A, Lucacchini A, Cassano GB, Martini C. Oxytocin receptor polymorphisms and adult attachment style in patients with depression. *Psychoneuroendocrinology* 2009; **34**: 1506-1514 [PMID: 19515497 DOI: 10.1016/j.psyneuen.2009.05.006]

40 **Monin JK**, Goktas SO, Kershaw T, DeWan A. Associations between spouses' oxytocin receptor gene polymorphism, attachment security, and marital satisfaction. *PLoS One* 2019; **14**: e0213083 [PMID: 30818381 DOI: 10.1371/journal.pone.0213083]

41 **Chen FS**, Johnson SC. An Oxytocin Receptor Gene Variant Predicts Attachment Anxiety in Females and Autism-Spectrum Traits in Males. *Soc Psychol Personal Sci* 2012; **3**: 93-99 [DOI: 10.1177/1948550611410325]

42 **Gillath O**, Shaver PR, Baek JM, Chun DS. Genetic correlates of adult attachment style. *Pers Soc Psychol Bull* 2008; **34**: 1396-1405 [PMID: 18687882 DOI: 10.1177/0146167208321484]

43 **Gong P**, Wang Q, Liu J, Xi S, Yang X, Fang P, Wang B, He L, Guo W, Zhang M. The OXTR polymorphisms are not associated with attachment dimensions: A three-approach study. *Psychoneuroendocrinology* 2020; **120**: 104780 [PMID: 32634747 DOI: 10.1016/j.psyneuen.2020.104780]

44 **Raby KL**, Cicchetti D, Carlson EA, Egeland B, Collins WA. Genetic contributions to continuity and change in attachment security: a prospective, longitudinal investigation from infancy to young adulthood. *J Child Psychol Psychiatry* 2013; **54**: 1223-1230 [PMID: 23731038 DOI: 10.1111/jcpp.12093]

45 **Fujiwara T**, Weisman O, Ochi M, Shirai K, Matsumoto K, Noguchi E, Feldman R. Genetic and peripheral markers of the oxytocin system and parental care jointly support the cross-generational transmission of bonding across three generations. *Psychoneuroendocrinology* 2019; **102**: 172-181 [PMID: 30572177 DOI: 10.1016/j.psyneuen.2018.12.004]

46 **Ebner NC**, Lin T, Muradoglu M, Weir DH, Plasencia GM, Lillard TS, Pournajafi-Nazarloo H, Cohen RA, Sue Carter C, Connelly JJ. Associations between oxytocin receptor gene (OXTR) methylation, plasma oxytocin, and attachment across adulthood. *Int J Psychophysiol* 2019; **136**: 22-32 [PMID: 29410310 DOI: 10.1016/j.ijpsycho.2018.01.008]

47 **Ein-Dor T**, Verbeke WJMI, Mokry M, Vrtička P. Epigenetic modification of the oxytocin and glucocorticoid receptor genes is linked to attachment avoidance in young adults. *Attach Hum Dev* 2018; **20**: 439-454 [PMID: 29513137 DOI: 10.1080/14616734.2018.1446451]

48 **Pohjalainen T**, Rinne JO, Någren K, Lehikoinen P, Anttila K, Syvälahti EK, Hietala J. The A1 allele of the human D2 dopamine receptor gene predicts low D2 receptor availability in healthy volunteers. *Mol Psychiatry* 1998; **3**: 256-260 [PMID: 9672901 DOI: 10.1038/sj.mp.4000350]

49 **Oak JN**, Oldenhof J, Van Tol HH. The dopamine D(4) receptor: one decade of research. *Eur J Pharmacol* 2000; **405**: 303-327 [PMID: 11033337 DOI: 10.1016/s0014-2999(00)00562-8]

50 **D'Souza UM**, Russ C, Tahir E, Mill J, McGuffin P, Asherson PJ, Craig IW. Functional effects of a tandem duplication polymorphism in the 5'flanking region of the DRD4 gene. *Biol Psychiatry* 2004; **56**: 691-697 [PMID: 15522254 DOI: 10.1016/j.biopsych.2004.08.008]

51 **Reiner I**, Spangler G. Adult attachment and gene polymorphisms of the dopamine D4 receptor and serotonin transporter (5-HTT). *Attach Hum Dev* 2010; **12**: 209-229 [PMID: 20473794 DOI: 10.1080/14616731003759674]

52 **Bakermans-Kranenburg MJ**, van IJzendoorn MH, Caspers K, Philibert R. DRD4 genotype moderates the impact of parental problems on unresolved loss or trauma. *Attach Hum Dev* 2011; **13**: 253-269 [PMID: 21506030 DOI: 10.1080/14616734.2011.562415]

53 **Witte AV**, Flöel A. Effects of COMT polymorphisms on brain function and behavior in health and disease. *Brain Res Bull* 2012; **88**: 418-428 [PMID: 22138198 DOI: 10.1016/j.brainresbull.2011.11.012]

54 **Comings DE**, MacMurray JP. Molecular heterosis: a review. *Mol Genet Metab* 2000; **71**: 19-31 [PMID: 11001792 DOI: 10.1006/mgme.2000.3015]

55 **Raby KL**, Cicchetti D, Carlson EA, Cutuli JJ, Englund MM, Egeland B. Genetic and caregiving-based contributions to infant attachment: unique associations with distress reactivity and attachment security. *Psychol Sci* 2012; **23**: 1016-1023 [PMID: 22829464 DOI: 10.1177/0956797612438265]

56 **Drago A**, Ronchi DD, Serretti A. 5-HT1A gene variants and psychiatric disorders: a review of current literature and selection of SNPs for future studies. *Int J Neuropsychopharmacol* 2008; **11**: 701-721 [PMID: 18047755 DOI: 10.1017/S1461145707008218]

57 **Lemonde S**, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, Sequeira A, Kushwaha N, Morris SJ, Basak A, Ou XM, Albert PR. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J Neurosci* 2003; **23**: 8788-8799 [PMID: 14507979 DOI: 10.1523/JNEUROSCI.23-25-08788.2003]

58 **Wu S**, Comings DE. A common C-1018G polymorphism in the human 5-HT1A receptor gene. *Psychiatr Genet* 1999; **9**: 105-106 [PMID: 10412191 DOI: 10.1097/00041444-199906000-00010]

59 **Czesak M**, Le François B, Millar AM, Deria M, Daigle M, Visvader JE, Anisman H, Albert PR. Increased serotonin-1A (5-HT1A) autoreceptor expression and reduced raphe serotonin levels in deformed epidermal autoregulatory factor-1 (Deaf-1) gene knock-out mice. *J Biol Chem* 2012; **287**: 6615-6627 [PMID: 22232550 DOI: 10.1074/jbc.M111.293027]

60 **Gong P**, Liu J, Li S, Zhou X. Serotonin receptor gene (5-HT1A) modulates alexithymic characteristics and attachment orientation. *Psychoneuroendocrinology* 2014; **50**: 274-279 [PMID: 25247748 DOI: 10.1016/j.psyneuen.2014.09.001]

61 **Turecki G**, Brière R, Dewar K, Antonetti T, Lesage AD, Séguin M, Chawky N, Vanier C, Alda M, Joober R, Benkelfat C, Rouleau GA. Prediction of level of serotonin 2A receptor binding by serotonin receptor 2A genetic variation in postmortem brain samples from subjects who did or did not commit suicide. *Am J Psychiatry* 1999; **156**: 1456-1458 [DOI: 10.1176/appi.ajp.158.1.148]

62 **Salo J**, Jokela M, Lehtimäki T, Keltikangas-Järvinen L. Serotonin receptor 2A gene moderates the effect of childhood maternal nurturance on adulthood social attachment. *Genes Brain Behav* 2011; **10**: 702-709 [PMID: 21649857 DOI: 10.1111/j.1601-183X.2011.00708.x]

63 **Lesch KP**, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996; **274**: 1527-1531 [PMID: 8929413 DOI: 10.1126/science.274.5292.1527]

64 **Caspers KM**, Paradiso S, Yucuis R, Troutman B, Arndt S, Philibert R. Association between the serotonin transporter promoter polymorphism (5-HTTLPR) and adult unresolved attachment. *Dev Psychol* 2009; **45**: 64-76 [PMID: 19209991 DOI: 10.1037/a0014026]

65 **van IJzendoorn MH**, Caspers K, Bakermans-Kranenburg MJ, Beach SR, Philibert R. Methylation matters: interaction between methylation density and serotonin transporter genotype predicts unresolved loss or trauma. *Biol Psychiatry* 2010; **68**: 405-407 [PMID: 20591416 DOI: 10.1016/j.biopsych.2010.05.008]

66 **Jones-Mason K**, Allen IE, Bush N, Hamilton S. Epigenetic marks as the link between environment and development: examination of the associations between attachment, socioeconomic status, and methylation of the SLC6A4 gene. *Brain Behav* 2016; **6**: e00480 [PMID: 27458544 DOI: 10.1002/brb3.480]

67 **Egan MF**, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003; **112**: 257-269 [PMID: 12553913 DOI: 10.1016/s0092-8674(03)00035-7]

68 **Suzuki A**, Matsumoto Y, Shibuya N, Ryoichi S, Kamata M, Enokido M, Goto K, Otani K. Interaction effect between the BDNF Val66Met polymorphism and parental rearing for interpersonal sensitivity in healthy subjects. *Psychiatry Res* 2012; **200**: 945-948 [PMID: 22542952 DOI: 10.1016/j.psychres.2012.03.014]

69 **Ibarra P**, Alemany S, Fatjó-Vilas M, Córdova-Palomera A, Goldberg X, Arias B, González-Ortega I, González-Pinto A, Nenadic I, Fañanás L. The BDNF-Val66Met polymorphism modulates parental rearing effects on adult psychiatric symptoms: a community twin-based study. *Eur Psychiatry* 2014; **29**: 293-300 [PMID: 24768157 DOI: 10.1016/j.eurpsy.2014.03.001]

70 **Oliveira P**, Fearon P. The biological bases of attachment. *Adopt Foster* 2019; **43**: 274-293 [DOI: 10.1177/0308575919867770]

71 **Bergen SE**, Gardner CO, Kendler KS. Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: a meta-analysis. *Twin Res Hum Genet* 2007; **10**: 423-433 [PMID: 17564500 DOI: 10.1375/twin.10.3.423]

72 **Haworth CM**, Kovas Y, Petrill SA, Plomin R. Developmental origins of low mathematics performance and normal variation in twins from 7 to 9 years. *Twin Res Hum Genet* 2007; **10**: 106-117 [PMID: 17539370 DOI: 10.1375/twin.10.1.106]

73 **Wadsworth SJ**, Corley RP, Hewitt JK, Defries JC; Colorado Adoption Project. Stability of genetic and environmental influences on reading performance at 7, 12, and 16 years of age in the Colorado Adoption Project. *Behav Genet* 2001; **31**: 353-359 [PMID: 11720121 DOI: 10.1023/a:1012218301437]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** bpgoffice@wjgnet.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2021 Baishideng Publishing Group Inc. All rights reserved.