






## Risk factors and genetic bases: the case of attention deficit hyperactivity disorder


### Factores de riesgo y bases genéticas: el caso del trastorno por déficit de atención e hiperactividad

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**ABSTRACT** Attention deficit hyperactivity disorder (ADHD) is considered to be the most frequent mental disorder in childhood. Although its diagnosis in the most utilized handbook of psychiatry in the world today – the *Diagnostic and statistical handbook of mental disorders* (DSM-5) – is based on behaviors of inattention, hyperactivity and impulsivity, numerous attempts to describe the biological bases of the disorder can be found, to be used for and also as risk markers. In this paper, we will critically analyze the validity of studies associated with the search for genetic markers of ADHD. First, a characterization of ADHD by the DSM-5 handbook is presented. Subsequently, the link between ADHD, risk factors and genetic markers is developed. Finally, some conclusions are presented which highlight simplifications and omissions that could have significant consequences.

**KEY WORDS** Attention Deficit Disorder with Hyperactivity; Risk Factors; Diagnostic and Statistical Handbook of Mental Disorders; Genetics; Genomics.

**RESUMEN** El trastorno por déficit de atención e hiperactividad (TDAH) es el trastorno mental considerado más frecuente en la infancia. Si bien su diagnóstico en el manual de psiquiatría hoy más utilizado en el mundo, el *Diagnostic and statistical handbook of mental disorders* (DSM-5), se basa en los comportamientos de desatención, hiperactividad e impulsividad, se encuentran numerosos intentos de describir las bases biológicas del trastorno para usarlos con fines de diagnóstico y como marcadores de riesgo. En este trabajo analizamos críticamente la validez de los estudios asociados a la búsqueda de marcadores genéticos para el TDAH. En primer lugar, se presenta la caracterización del TDAH en el DSM-5; luego, se desarrolla el vínculo entre el TDAH, los factores de riesgo y los marcadores genéticos; y, finalmente, se presentan algunas conclusiones en las que se señalan simplificaciones y omisiones que pueden tener consecuencias significativas.

**PALABRAS CLAVES** Trastorno por Déficit de Atención con Hiperactividad; Factores de Riesgo; Handbook Diagnóstico y Estadístico de los Trastornos Mentales; Genética; Genómica.

## INTRODUCTION

The existence of unstable, blurred, and ambiguous boundaries between the normal and the pathological in the field of mental health led to the acceptance of a process by which typical childhood behaviors began to be identified as abnormal. In this way, an area of knowledge and intervention was consolidated, described by Michel Foucault<sup>(1)</sup> as medicine of the non-pathological. Within this framework, over the last decades, a group of typical childhood behaviors has been integrated into the psychiatric logic of risk. According to this logic, to avoid the chronification of mental disorders in adulthood, it is necessary to diagnose small deviations already exhibited during preschool age. In fact, the obsession with detecting mental disorders in childhood at an early stage seems to be the core around which the *Diagnostic and Statistical Handbook of Mental Disorders* (DSM-5) pivots. This strategy is practically present in every mental disorder described in the handbook, and has augmented a tendency already introduced in previous handbooks to predict and prevent risks at increasingly early ages.

Attention deficit hyperactivity disorder (ADHD) is considered to be the most common mental disorder in childhood, and its diagnosis in the DSM-5 is based on behaviors of inattention, hyperactivity, and impulsivity. As there are no laboratory tests to detect this pathology, the diagnosis is clinically made. As a result, any person can be easily diagnosed with this mental disorder, and receive a methylphenidate prescription.<sup>(2)</sup> The result of this vulnerability in diagnosis is a significant number of individuals receiving a false positive diagnosis, since it affects between 5% and 10% of children and adolescents in several continents.<sup>(2,3,4,5)</sup>

Over the last few years, several attempts have been made to describe the biological bases of the disorder, to use them for the purposes of diagnosis and also as risk markers. In fact, the DSM-5 refers to the need to establish ways of identifying potential risks related to individuals developing mental disorders,

not only for ADHD but for almost all classified psychiatric diseases. Detecting risks for ADHD supposes the existence of biological markers, in particular genetic markers, as a potentially fertile tool for early detection of the disorder, thus guaranteeing a better treatment and recovery.

In this paper, we will critically analyze research studies associated with the search for genetic markers of ADHD. To achieve this, a series of arguments will be concatenated including the characterization of ADHD in the DSM-5, and an analysis of the seemingly existing links with some risk factors. Finally, explanations referring to supposed biological makers of the disorder will be scrutinized, in particular markers related to genetic and genomic aspects.

## ADHD AS DESCRIBED IN THE DIAGNOSTIC AND STATISTICAL HANDBOOK OF MENTAL DISORDERS (DSM-5)

The ambition of the DSM-5 to predict potential risks of individuals developing mental disorders in the future attracted great criticism, the strongest of which was made by Allen Frances in his book *Saving normal: An insider's look at the epidemic of mental illness*.<sup>(2)</sup> Frances, who was the chair of the Task Force at the American Psychiatric Association (APA) that organized the DSM-IV, argues that, inasmuch as there are no biological markers defined for childhood mental illnesses that validate clusters of symptoms, one could easily combine them in the endless ways possible, leading to new diagnoses. Frances considers that, given the existing difficulty in establishing precise limits between normality and psychiatric pathology, the classification of diagnoses for mental disorders can be indefinitely expanded; therefore for each new release, new diagnoses and wider symptom clustering appear, as in the case of the so-called "autism spectrum disorder."

In particular, the diagnosis that worried Frances the most was the "psychosis risk

syndrome.” In fact, this category was excluded from the DSM-5, but it reappeared under the label “attenuated psychosis syndrome,” and it was included within the group of schizophrenia spectrum disorders.<sup>(3)</sup> In this sense, Frances states that:

The only way to avoid the perils of DSM-5 is to be fully aware of them. It makes absolutely no sense to pin the misleading and stigmatizing label “Other Specified Schizophrenia Spectrum Disorder” on someone who, in typical settings, will have only about a 10% chance of ever becoming psychotic. And certainly it makes no sense to follow this misdiagnosis with an unproven and potentially very harmful antipsychotic treatment.<sup>(6)</sup>

In several papers, Frances states that the DSM-5 anticipates the appearance of a true pandemic of mental disorders.<sup>(2,6,7)</sup> In this way, according to Allen Frances, the peril behind the DSM-5 is the creation of millions of new “false positive patients,” exacerbating the problems caused by previous handbooks. Therefore massive and unnecessary treatments would come into existence, with costly and highly harmful drugs.<sup>(2,7)</sup>

The Brazilian Association of Attention Deficit says that, among the several factors causing ADHD, two are fundamental. On the one hand, it affirms the existence of a genetic predisposition:

What happens in these disorders is that the genetic predisposition involves several genes, and not a single gene (which is the rule in many of our physical characteristics as well). Probably no unique “ADHD gene” exists, at least it is believed that no such gene exists. Furthermore, genes can have different levels of activity, some can act in some patients in a different way than in others; they interact among themselves, adding also the influence of environmental factors. [O que acontece nestes transtornos é que a predisposição genética envolve vários genes, e não um único gene (como é a

regra para várias de nossas características físicas, também). Provavelmente não existe, ou não se acredita que exista, um único “gene do TDAH”. Além disto, genes podem ter diferentes níveis de atividade, alguns podem estar agindo em alguns pacientes de um modo diferente que em outros; eles interagem entre si, somando-se ainda as influências ambientais].<sup>(8)</sup>

On the other hand, the Association maintains that it is a disorder caused by neurochemical alterations, saying that:

What seems to be altered in this brain region is the functioning of a system of chemical substances called neurotransmitters (namely dopamine and noradrenaline), which pass information among the nerve cells (neurons). There are causes that have been investigated in relation to these changes in neurotransmitters of the frontal region and their connections. [O que parece estar alterado nesta região cerebral é o funcionamento de um sistema de substâncias químicas chamadas neurotransmissores (principalmente dopamina e noradrenalina), que passam informação entre as células nervosas (neurônios). Existem causas que foram investigadas para estas alterações nos neurotransmissores da região frontal e suas conexões].<sup>(8)</sup>

In the DSM-5, ADHD is classified as a neurodevelopmental disorder. However, in principle, this does not mean that there is indeed a neurological alteration in a certain region of the brain, or a neurophysiological deficit, because the handbook mentions that, at present, biological makers of ADHD have not been identified.<sup>(3)</sup> In medicine, the term “development” means:

...a natural process of progression from a previous, lower, embryonic, or juvenile state, into a higher, later, more complex, or adult state. [...o processo natural de progressão de um estado anterior,

*inferior, embrionário ou juvenil, para outro superior, posterior mais complexo, ou estado adulto*].<sup>(9)</sup>

In the case of a child, child development is understood as

*...a process of knowledge acquisition, in the broadest sense, including perception, memory, discernment, and reason. [...processo de aquisição de conhecimento, no sentido amplo, incluindo percepção, memória, discernimento e raciocínio]*.<sup>(9)</sup>

The prefix “neuro” refers to the nervous system; therefore, the term neurodevelopment is quite a broad term including various aspects related to all disorders comprised in the DSM-5, in addition to behaviors referring to ADHD. The manner in which this pathology is described in the handbook can lead to an understanding that this term refers specifically to problems in the brain, although it is in fact related to broader aspects than the brain. The handbook itself states that “neurodevelopmental disorders are a group of conditions with onset in the developmental period.”<sup>(3)</sup>

Various researches are analyzing whether there is any link between the behavior of children with ADHD and a potential alteration in the brain or any type of genetic alteration; however, the DSM-5 does not mention any conclusive study. According to Polanczyk, at present there are no biological or electrophysiological markers, not even through neuroimaging, that are clinically useful for ADHD diagnosis purposes.<sup>(10)</sup>

According to the DSM 5, the problems presented by neurodevelopmental disorders affect personal, social, and school relationships in childhood, and occupational relationships in adulthood. As stated in the handbook:

*The disorders typically manifest early in development, often before the child enters grade school, and are characterized by developmental deficits that produce impairments of personal, social, academic, or occupational functioning.*<sup>(3)</sup>

It is understood that, during this period, the child comes across adversities typical of their developmental process, which are simply life stages to be surpassed. According to the DSM-5, “ADHD is a neurodevelopmental disorder defined by impairing levels of inattention, disorganization, and/or hyperactivity-impulsivity.”<sup>(3)</sup> As can be seen, none of these aspects referring to a child’s behavior are necessarily related to some kind of neurological problem.

As regards the criteria to determine an ADHD diagnosis, the DSM-5 affirms that given a list of nine symptoms for inattention, and nine symptoms for hyperactivity, the persistence of six symptoms from each group for a period of six months will indicate the existence of the disorder. It is also said that those behaviors may be indicative of an ADHD diagnosis, if they are inconsistent with developmental level, or if they negatively impact upon social, academic, and occupational activities.

The symptoms defined by the DSM-5 for the diagnosis of inattention, in the so-called *Criterion A1*, are as follows:

- (a) Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities [...].
- (b) Often has difficulty sustaining attention in tasks or play activities [...].
- (c) Often does not seem to listen when spoken to directly [...].
- (d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace [...].
- (e) Often has difficulty organizing tasks and activities [...].
- (f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort [...].
- (g) Often loses things necessary for tasks or activities [...].
- (h) Is often easily distracted by extraneous stimuli [...].
- (i) Is often forgetful in daily activities [...].<sup>(3)</sup>

The symptoms defined by the DSM-5 for the diagnosis of hyperactivity, in the so-called *Criterion A2*, are as follows:

(a) Often fidgets with or taps hands or feet or squirms in seat. (b) Often leaves seat in situations when remaining seated is expected [...]. (c) Often runs about or climbs in situations where it is inappropriate. [...]. (d) Often unable to play or engage in leisure activities quietly. (e) Is often "on the go," acting as if "driven by a motor" [...]. (f) Often talks excessively. (g) Often blurts out an answer before a question has been completed [...]. (h) Often has difficulty waiting his or her turn [...]. (i) Often interrupts or intrudes on others [...].<sup>(3)</sup>

Considering these two clusters of symptoms, and if there is a predominance of *Criterion A1* or *Criterion A2*, three subtypes within the ADHD diagnosis are identified: (a) inattention and hyperactivity combined type, with the code 314.02 of the DSM-5; (b) predominantly inattentive type, with a preponderance of symptoms described in *Criterion A1*, with the code 314.00; (c) predominantly hyperactive type, with a preponderance of symptoms described in *Criterion A2*, with the code 314.01.<sup>(3)</sup>

Focusing on each symptom of ADHD in depth, when it comes to inattention and disorganization symptoms, the DSM-5 states that "they imply inability to stay on task, seeming not to listen, and losing materials, at levels that are inconsistent with age or developmental levels."<sup>(3)</sup> The handbook does not specify the type of task being alluded to, or in which situation the child does not seem to listen, nor does it explain what developmental levels are considered normal for the age. These situations would quite probably involve tasks that are not of the child's interest so as to sustain their attention or to organize themselves for that activity.

In relation to hyperactivity-impulsivity symptoms, the handbook affirms that "this refers to excessive motor activity, excessive fidgeting, extreme restlessness, or interrupting others' activities, and inability to wait for their turn in an excessive way for the age or developmental level."<sup>(3)</sup> The first question relating to those symptoms is whether one can

have an exact measurement to determine the behavior of each child, when referring to ambiguous symptoms such as "excessive motor activity," "inability to remain seated," "interrupting others' activities," or "inability to wait for their turn."<sup>(3)</sup>

According to the DSM-5, the symptoms should occur before the age of 12 years. Perhaps for that reason ADHD is known as a school age disorder, though it can be detected at school and at home. According to the DSM-5, with respect to the setting in which the symptoms are identified, the so-called "disorder manifestations" must be present in more than one setting, for instance, at home and at school. The identification of these behaviors is carried out by informants that observe the children: "Confirmation of substantial symptoms across settings typically cannot be done accurately without consulting informants who have seen the individual in those settings."<sup>(3)</sup> In other words, the parameter depends on the judgment of somebody who is observing the child, and not subject to a direct evaluation of the behavior by a health care professional, or by some type of test. This particular feature of the ADHD diagnosis is relevant since the behavior of children tends to vary if the activity performed is of their interest or not, and whether the setting where the child is located is favorable or not.

In this situation, Becker's words are of great significance, when he affirms that:

...social groups create deviance by making the rules ... deviance is not a quality of the act the person commits, but rather a consequence of the application by others of rules and sanctions to an "offender." [...os grupos sociais criam o desvio ao fazer as regras [...] o desvio não é uma qualidade do ato que a pessoa comete, mas uma consequência da aplicação por outras pessoas de regras e sanções a um transgressor].<sup>(11)</sup>

When establishing rules, society seeks to categorize, among all the people, those that deviate from the system, those who will

be labeled and categorized according to standards.

Indeed, even when the DSM-5 classifies ADHD as a neurodevelopmental disorder, it is easy to observe that the disorder refers to symptoms that are inherent in childhood behaviors. Therefore, conducts such as inattention, hyperactivity, and impulsivity become symptoms of a disorder through the look that an adult directs at a child. All these seem to indicate that this type of diagnosis is fragile, since there are huge epistemological inaccuracies, despite the fact that the therapy prescribed for such an ambiguous disorder is a psychopharmacological treatment.

## ADHD AND RISK FACTORS

The DSM-5 describes “risk and prognostic factors” related to ADHD. Temperamental, environmental, genetic, and physiological factors are mentioned.<sup>(3)</sup> Although the handbook refers to probabilities, stating that these factors would suggest the presence of the disorder, it does not affirm that there is a direct or causal relationship among those factors and the disorder.

Temperamental factors mentioned in the DSM-5 are linked to aspects that are not specific to ADHD, such as reduced levels of behavioral inhibition, effortful control or constraint, elevated novelty seeking, among other factors. Regarding environmental factors, the handbook refers to the existence of ambiguous and varied correlations with: (a) very low birth weight, although most children with this characteristic do not develop ADHD; (b) use of tobacco during pregnancy; (c) dietary associations; (d) aspects related to life history, such as child abuse, neglect, or multiple foster placements; (e) neurotoxin exposure, infections, or alcohol exposure in utero.<sup>(3)</sup> Said factors are claimed to be potentially correlated with subsequent ADHD, but there is no clear evidence that these are causal factors.

Regarding genetic and physiological factors, the handbook mentions that “it is more

prevalent among the first-degree biological relatives of individuals with ADHD,” and that specific genes have been correlated with this disorder.<sup>(3)</sup> With respect to physiological factors considered to be possible influences on ADHD symptoms, the handbook mentions “visual and hearing impairments, metabolic abnormalities, sleep disorders, nutritional deficiencies, and epilepsy.”<sup>(3)</sup> Although these circumstances may produce some damage to the individual having those problems, the handbook fails to explain how they can influence the diagnosis of ADHD. For instance, a child that has hearing impairment perhaps does not remain seated or attentive in class, but this does not mean that the behavior is related to ADHD symptoms. Similarly, if a child does not manage to get adequate sleep, they will probably exhibit an attention deficit during school classes. These examples challenge the idea that those factors can influence the onset of ADHD symptoms. Finally, and despite the inexistence of any associations between ADHD and specific physical characteristics, the DSM-5 mentions “minor physical anomalies” such as: hypertelorism, highly arched palate, low-set ears;<sup>(3)</sup> anomalies clearly stigmatizing for the subject.

We can see that the DSM-5 takes a wide range of factors as potential or possible causes of ADHD, ranging from the use of alcohol or tobacco during pregnancy, very low birth weight, existence of physiological problems such as motor delays, and even supposed genetic factors. The central influence given to these potential biological factors results in limiting and disregarding the influence that family or school conflicts may have over a child’s behavior, as well as the suffering that those conflicts may cause in early childhood. The handbook also fails to consider that those behaviors can be the symbolic response available to a child to face a situation he or she considers adverse.

From a risk perspective, it seems that practically all the factors that are stressors could lead to ADHD. This situation gives rise to a lot of questions regarding the factors described in the DSM-5. Our perception in this sense is that there are no strongly substantiated factors, but

rather probabilities of situations that may or may not occur. As the DSM-5 is written based on the findings of research studies, it is believed that it is possible, and even important, to investigate all the factors that may be associated with any mental disorder. That does not mean that the investigated aspects represent risk factors because, if proven, they would be factors related to the disorder, but not risk factors. The idea of risk implies probabilities, possible factors provoking a disease, but it is also assumed that correlations may not occur. In this sense, everything seems to indicate that, with respect to ADHD, the idea of risk constitutes a fallacy.

It is under this scenario, where it is possible to identify mechanisms of risk and certainty, that one can talk about biopolitical strategies of control. Hence, by disseminating these “risks” that are characterized as true threats for adulthood, any identification of a disorder in childhood seems to be legitimized. It is possible to affirm that:

...the security device, with its statistical studies of prediction and prevention of risks, is the main element with which to understand the articulation between biopolitics and psychiatrization of society in our contemporary world. [...o dispositivo de segurança, com seus estudos estatísticos de antecipação e prevenção de riscos, é o elemento central para compreender a articulação entre biopolítica e psiquiatrização da sociedade no mundo contemporâneo].<sup>(12)</sup>

Following this logic, any unwanted behavior can be considered a deviation and indicative of some mental disorder.

## ADHD, RISK FACTORS AND BIOLOGICAL SUBSTRATES

In order to avoid ambiguous psychiatric diagnoses based on symptoms, over the last years there has been a growing tendency to look for biological explanations for mental disorders.

Furthermore, if those biological markers of mental disorders can be defined, early detection of mental disorders could then end up having the same value and the same predictive rigor as any preventive test, just like hearing and vision tests, head circumference measurement to detect microcephaly, among others. Therefore, potential biological markers of the disorder would play a central role when defining diagnoses and risk factors.

In principle, and as a general rule, a considerable amount of research on biological bases for ADHD attempt to recognize some type of correlation between the diagnosis of ADHD and certain biological traits. This is basically done by analyzing whether the group affected by the disorder is different from a non-affected group regarding some specific biological characteristics. With this aim, different variables are measured in children, among which there can be found the size and shape of the brain, or some of its parts, the activity of a brain area or circuit, or the presence of particular genetic variants. We will briefly see some characteristics and drawbacks of research studies that look for biological substrates and risk factors, mainly genetic and genomic.

## Genetic bases

As far as genetics is concerned, the DSM-5 mentions that even “in the uncommon cases where there is a known genetic cause (e.g., Fragile X syndrome, 22q11 deletion syndrome), the ADHD presentation should still be diagnosed.”<sup>(3)</sup> This means that, in very limited cases in which a relationship between ADHD with some genetic aspect was found, this would show that in individuals sharing the genetic trait, for instance, Fragile X syndrome, there may also be ADHD symptoms – such as inattention, hyperactivity, and impulsivity – however this does not imply that the diagnosis of ADHD can be made based on such genetic trait, but rather will have to be diagnosed separately.

The publications that we analyzed describe research studies on genetic aspects

associated with ADHD and have the following characteristics. Most research studies affirm that ADHD has a “substantial genetic component.”<sup>(13)</sup> In the same way, Pauls maintains that it is clear that ADHD is a genetically complex disorder,<sup>(14)</sup> while Smoot et al. state that there would be a genetic cause in approximately 75% of ADHD cases.<sup>(15)</sup> As noted above, most of these research studies are based on the strategy of recognizing some type of correlation between the diagnosis of ADHD and the presence of particular genetic variants. More specifically, these studies seek to find alleles of genes associated with the presence of the disorder. Therefore, for the genes identified, at least two segregating variants in a given population (i.e., alleles) are known. If an individual carries one of those alleles, they would have a greater risk of being diagnosed with ADHD compared to those who do not carry it. Such an allele is referred to as a “risk allele.” Genetic studies on ADHD focus mainly on particular genes, whose function is known in advance, and it is assumed that as a result of performing that function they could be associated with a hypothetical ADHD pathophysiology.

This methodological approach is different from a number of genomic studies that are described below. As regards classical genetics, most research studies have focused on dopaminergic pathway genes: dopamine receptors, transmitters, and enzymes involved in its metabolism.<sup>(16,17,18)</sup> A specific allele of the dopamine receptor D4 gene is particularly relevant – see, for instance, the work by Bellgrove et al.,<sup>(19)</sup> Kieling et al.,<sup>(20)</sup> and Swanson et al.<sup>(21)</sup> Similarly, other proposals of candidate genes with a smaller number of genetic studies have been acknowledged, those related to the metabolism of the noradrenaline neurotransmitter.<sup>(22)</sup> Less acknowledged propositions still link ADHD with a different neurotransmitter, serotonin<sup>(23)</sup>; leading to a small number of genetic studies related to its metabolism. In turn, there are other studies that analyze the relationship between ADHD and genes related to ethanol metabolism.<sup>(24)</sup>

Finally, another genetic approach uses animal models in search for ADHD genetic

bases. These research studies assume that model animals have behaviors that can be extrapolated to behaviors that define ADHD in humans, as in the case of rats<sup>(13)</sup> and mice.<sup>(25)</sup> Inevitably, based on the symptoms proposed by the DSM-5, the studies using this methodological tool necessarily have to create new criteria to determine whether model animals can be homologous with human individuals diagnosed with ADHD. As a result, new criteria have been developed such as separation from the walls of a box, when these animals move forward, and how much they raise their head, among others.<sup>(13,25)</sup> The second step in these studies is to relate atypical behaviors in these animals to their genes. Researchers who work with animal models – see, for instance, the works by Vendruscolo et al.,<sup>(13)</sup> Faraone et al.,<sup>(18)</sup> Gainetdinov et al.,<sup>(25)</sup> van der Kooij et al.,<sup>(26)</sup> – assume that there are particular genetic traits that account for atypical behaviors.

Research studies that deal with ADHD genetic bases, considered to be relevant risk indicators, present a number of difficulties, namely methodological problems and epistemological bias. In the first place, research in humans is based on significant and inevitable age and sex heterogeneity, and the studies may even have participants that took part in previous pharmacologic treatments. Regarding this latter source of heterogeneity, children participating in the studies as diagnosed with the disorder may be medicated or non-medicated; and if they are medicated, they could have been treated with different drugs.<sup>(27)</sup> Some authors – for instance, Rodríguez Ponte,<sup>(28)</sup> Janin,<sup>(29)</sup> Janin,<sup>(30)</sup> Silver,<sup>(31)</sup> Levin,<sup>(32)</sup> Dueñas,<sup>(33)</sup> Filidoro<sup>(34)</sup> – have highlighted that there is another heterogeneity source within the group of children with ADHD, in which they can identify several and various problems, regarding the history and particular context of each child. Consequently, in the experimental group of children affected with ADHD, there would be various sources of heterogeneity that are not generally considered in genetic studies. The problem associated with heterogeneity is that, if necessary precautions are not taken in order to identify it, it will have a direct impact on the findings of the

experiments. This problem was highlighted by some authors, for instance, Swanson et al.,<sup>(22)</sup> who have noted that the scope of the results will be limited in those studies involving groups of fewer than 50 children with ADHD, because experimental groups are too prone to internal heterogeneities. In other words, the influence of one of the above-mentioned factors becomes very relevant in small samples, where it would be impossible to distinguish whether the correlation between genetic traits in question is with the diagnosis of ADHD or with the factor not taken into account. In order to answer this type of question, meta-analysis studies<sup>(17,35,36)</sup> have been conducted, which review a group of studies such as the ones mentioned here. These meta-analysis studies consist in taking similar studies with small-sized samples and analyzing them as a whole. Hence, where individual results had a limited scope because of the small size of the samples, the result of the whole set of the studies would have a greater scope. However, these meta-analysis studies do not usually take into account the particular characteristics of each sample, and quite often they even fail to mention many of those particular features. Furthermore, they compile studies conducted in different countries, and fail to consider geographical variations in the diagnosis of ADHD that are reported in several sources.<sup>(8,37,38)</sup> For instance, Moffitt and Melchior report that the number of children affected with ADHD can vary among countries from 6.2% to 11.8%.<sup>(37)</sup> Therefore, the heterogeneity problem becomes more complex, because neither the location nor the inclusion criteria in each study are taken into account. In other words, although there is heterogeneity in each study, there are also differences among them. The omission and concealment of multiple heterogeneities and the resulting problem in methodologically weakening the configuration of ADHD genetic bases is one of the topics that can be identified, but it is not the only one.

The other important bias has to do with the way that the genetic molecular domain is conceptualized. Although, from a discursive perspective, the genetic complexity of this disorder is acknowledged, this is not

taken into account in the design of studies, in which a number of implications with respect to the actions of the genes in the context of ADHD is assumed. Although, as we have mentioned above, it has been suggested that several genes could be related to ADHD, most research studies are only focused on one or a few of them, and the interactions among genes are seldom studied. For instance, Kieling et al. highlight in the introduction of their work that the disorder presents a “complex nature, both at the genotypic (multiple genes) and the phenotypic (phenomenological heterogeneity) levels.”<sup>(20)</sup> However, this study analyses the association between a single gene and the performance in a neuropsychological test. Another example is given by Swanson et al., where also a study of the correlation between a gene and individuals responses in neuropsychological tests is shown.<sup>(35)</sup> In addition, these research studies do not consider important interactions that take place between the genotype and the environment, one of the greatest theoretical contributions in biology from the 1980s onward. As explained by Kaplan, “the relationship between the genotype and the phenotype is plastic – capable of varying based on developmental environment.”<sup>(39)</sup> Hence, the contribution of environmental factors are not taken into account when designing research studies. This problem is highlighted by some authors in charge of reviewing research on ADHD. For instance, Swanson et al. show in their work that “few molecular genetic studies of ADHD have addressed gene-environment interactions.”<sup>(22)</sup> Along the same lines, Pauls concludes that “most genetic researchers acknowledge that it is important to assess environmental factors in genetic studies; however, very few studies have been able to adequately measure environmental factors.”<sup>(14)</sup> Out of the works analyzed, only one reference was detected in the study by Swanson et al.<sup>(22)</sup> where it was stated that epigenetic variation could provide some explanations for ADHD. Therefore, both in their functional aspects of regulation of gene expression as a possible functional cause of disorder manifestation, and in their role in

the so-called epigenetic inheritance, these developments of Biology over the last years have not been included in neurobiology research studies dealing with ADHD. As a result, a simplified relationship between a gene and the disorder is shown, in terms of an overall unitary relationship that is, in addition, described as linear and separate from its environmental, genetic, and epigenetic settings.

From this perspective, in general, what prevails is the notion that the results obtained in genetic studies on ADHD are hardly conclusive, presenting marked conceptual slants. Swanson et al. highlight that “the existing studies of genetic and environmental factors do not meet the standards for modern molecular genetic studies.”<sup>(22)</sup> These authors also state that “gene-gene and gene-environment interactions are likely to be present and require large sample size to detect and describe. [...] most current studies fail to address the known and expected complexity of gene-gene and gene-environment interactions that has emerged in research of other complex disorders.”<sup>(22)</sup>

### Genomic bases

The first genomic study on ADHD was conducted in 2003, only two years after the release of the first draft of the human genome. Over the last few years, the volume of both genomic data in humans and methodological developments for its analysis have increased enormously. It is in this context that different genomic studies on ADHD have been carried out, and around thirty have been released so far (see, for instance, reviews by Franke et al.,<sup>(40)</sup> and Hawi et al.<sup>(41)</sup>). These studies used different genomic methodologies involving different experimental designs, as well as various statistical analyses and a progressive increase in sample sizes. The methodology used in most of the studies is the *genome-wide association study* (GWAS). GWAS studies involve establishing a statistical association between genomic variants that can be placed anywhere in the genome, and some phenotypic trait of the organism in question. In general, genomic

variants are single nucleotide polymorphisms (SNP), which occur at a *specific* position in the *genome* — a nucleotide — and not all the individuals of the population share the same nucleotide base (there are four types of nucleotide bases in DNA). The phenotypic characteristic can be morphologic, behavioral, etc.; or a disease, a disorder, or pathology. Although GWAS is a very powerful and sophisticated methodological and statistical technique, its logic is very simple: if individuals with a particular phenotypic characteristic have, in a bigger proportion than the expected by chance, a particular genomic variant then this variant would be associated with the phenotypic characteristic. With respect to the general logic of genomic studies on ADHD, all research studies use one of two strategies, and in some cases both strategies are used in the same study: on the one hand, there are works searching for genes at a genomic level, or any other genomic element associated with ADHD without basing this search on theories that conceptualize the disorder in any specific way, the so-called *hypothesis-free analyses*; on the other hand, there are also studies in which researchers look for the association of particular genes of interest with ADHD, the selection of these genes being based on previous theories and studies.

In principle, it should be noted that the findings obtained in most of the genomic studies on ADHD, when it comes to recognizing genes or genomic variants associated with the disorder, are almost null. The above-mentioned reviews clearly state that “taking together all results from the GWAS performed in ADHD, the following is to be remarked: none of the findings so far show genome-wide significant association with ADHD according to the thresholds currently handled”<sup>(40)</sup> and “overall ADHD-GWA studies have had limited success in identifying associations at the critical significance level.”<sup>(41)</sup> Although it is acknowledged that “currently, we do not have sufficient information to draw strong conclusions about the relative impact of the biological pathways and genetic influences,”<sup>(40)</sup> it is argued that the problem with these studies is that they would not detect

low-frequency genetic variants, which could indeed be associated with ADHD; variants with very small effects on the phenotype of ADHD are not being studied either.<sup>(40,42)</sup> In this sense, the latest research was based on studying the association between ADHD and genomic elements called copy number variations (CNV), these genomic elements have lower frequencies than the ones studied so far. These studies have found some associations, however "...the majority of CNVs implicated thus far in ADHD are evidently not highly penetrant (that is, not causally linked to ADHD) as they were also detected (albeit less frequently) in control samples. [...] most of the reported CNVs show limited intersection between individual patients, meaning that any one rare variant identified in a particular individual with ADHD may have limited explanatory value for the broader ADHD population."<sup>(41)</sup> Beyond the discussion of main findings, this analysis serves to highlight conceptualizations, problems, and omissions in genomic studies when dealing with ADHD. In principle, the problems with these research studies are not sample sizes; although early studies or those focused on a particular population could be criticized for not having a sufficient number of individuals to provide the analysis with the required power to detect low-frequency variants associated with ADHD in a population, meta-analyses of genomic databases have been conducted, and also studies using genomic data of consortium research initiatives with thousands of genomes that amount to sample sizes large enough to solve this problem.<sup>(40,41)</sup> However, a new problem pertaining to heterogeneity emerges when neither the location nor the inclusion criteria in each study are taken into account in the meta-analyses or in the data bases of genomic consortia. That is, the omission and concealment of heterogeneity in these studies methodologically weakens the configuration of the genomic bases for ADHD.

In addition, it should be emphasized that in studies presenting inconclusive and non-robust results promises regarding the genomic bases for ADHD can be found. For instance, Franke et al. reported that "For now, GWAS

holds the greatest promise for understanding the genetic architecture of ADHD! However, we need to improve the design of these studies by increasing sample size for more power and by further improving/extending phenotypic assessment to better reflect and partition the phenotypic complexity of the disorder."<sup>(40)</sup> That is, the following step seems to be the performance of studies dealing with the association between genomic elements with phenotypes of children different from the phenotypes that had been used, basically endophenotypes that may be quantified by means of any neurobiological methodology that would represent the diagnosis of the disorder based on symptoms. This is clearly expressed in the review by Hawi et al.: "Whereas the vast majority of genetic studies have treated ADHD as a unitary construct, we argue that a shift towards heterogeneity reduction, including the use of empirically derived endophenotypes and data-driven classification techniques, must now be used to advance the field."<sup>(41)</sup> We understand that this subsequent appeal to a promise that in the future genomic bases for ADHD may be found can be related to the acceptance and potentiality of genomic elements as indicators of risk.

All in all, just like in non-genomic genetic studies, genomic studies on ADHD present non-robust and completely inconclusive results; at the same time they all have methodological and conceptual biases and simplifications. The latter can be clearly observed in the fact that, except in one article where the interaction of the genome with the environment is studied and where possible non-genetic effects are mentioned,<sup>(43)</sup> and another study in which interaction analyses known as *pathway analysis*<sup>(44)</sup> are performed, most of the studies are focused on detecting individual genes related to ADHD, which could later be presented as genes that are causally involved in ADHD, apart from being risk markers of the disorder. That is, a simplified relationship is shown, in the sense of an overall, unitary relationship between the gene and the disorder that is also described as linear and isolated from environmental, genetic, and epigenetic contexts.

## CONCLUSIONS AND DISCUSSION: SIMPLIFICATIONS AND OMISSIONS

Arguments were presented throughout this work to show that over the last few years the interest in describing biological bases for ADHD can be framed in terms of their use for diagnosis purposes, and also as risk markers of the disorder. However, it has also been established that studies on biological bases for ADHD – in particular, genetic and genomic studies – show some problems. In principle, and generally speaking, the diagnosis of ADHD by means of behavioral symptoms as proposed in the DSM-5 seems to include symptoms that would be behaviors pertaining to the children's world in general. However, such behaviors of inattention, hyperactivity, and impulsivity typical of childhood behavior and its complexities, become indicators of a disorder through the look that an adult directs at a child. This constitutes a weakness or bias in the diagnosis that cannot be disregarded.

Nevertheless, the DSM-5 does not just present descriptive diagnoses from a set of symptoms, but also describes "risk and prognostic factors" of ADHD, taking as a reference supposed biological bases for the disorder. These factors are temperamental, environmental, genetic, and physiological. We enumerated several problems in relation to these "risk factors," because there is no clear evidence to confirm a direct relationship between these factors and the disorder. We observe that underlying these criteria are social situations that undoubtedly need attention since they create psychic suffering. Indeed, it is important to highlight that social problems cause a psychic suffering in the subject, causing the display behaviors of impulsivity, inattention, hyperactivity, sadness, among others. This does not mean that if during a period of five or six months, as is established for the diagnosis of ADHD, the individual does not overcome these difficulties and there are still manifestations of these behaviors, it would be necessary to receive the diagnosis of a mental disorder. The main treatment for ADHD is methylphenidate,

a drug requiring medical prescription to be dispensed. One should wonder whether it would be adequate to treat such complex social issues as the ones described here with a medication.

In this scenario, and given the ambiguity of the diagnosis, it is necessary to legitimate interventions based on biological, neurobiological, and genetic explanations for mental disorders. The argument is that if it were possible to find such causal explanations, the ambiguity of the diagnosis would decrease, since clear biological parameters would exist, just as in other areas of medicine. Furthermore, these potential biological markers of the disorder would play a role within the schema of risk factors for early detection and a timely treatment of the disorder.

However, we found that genetic and genomic studies on ADHD present non-robust and completely inconclusive results, and that, at the same time, those studies have methodological and conceptual biases and simplifications. Mainly we found that those studies show results with methodological problems, and where these problems are overcome, mainly in genomic studies, the results are quite inconclusive regarding the relationship of ADHD with biological substrates, genomic in this case. Even given a scenario clear of these problems, we nevertheless found a predominance of a simplified conceptualization of the genetic bases of the disorder, in the sense of an overall, unitary relationship between a gene and the disorder that is also described as linear and separate from the environmental, genetic, and epigenetic settings. That is, even if empirical evidence on genetic and genomic bases for ADHD were solid, there would be a simplified conceptualization with omissions. We propose a critical look here because we understand that the result of searching for genetic and genomic bases would be an even greater increase in the number of children diagnosed with ADHD, based on the idea that there are genetic or genomic risk factors that would facilitate the detection of the disease at increasingly earlier ages. In the same way, the use of psychotropic drugs as a predominant treatment would

be more sustainable under simplified genetic and genomic scenarios, in which the genetic causes are unitary and, as a consequence, more directly treated by drugs acting on the gene product.

Therefore, the analysis presented here shows that epistemic aspects, simplifications, and omissions regarding the genetic bases for ADHD become relevant in two points as far as ADHD problems are concerned: risk and therapeutics. The identified problems, referring to the genetic bases for ADHD, call for a critical look with respect to this knowledge to carefully assess its role as a possible source of diagnoses free of ambiguities, and as substrate in which to look for early risk markers

of ADHD. It is necessary to wonder what science is being produced from handbooks like the DSM-5, and who this science is really serving, even when it is knowledge that is accepted by the most well-known scientific circles. Once more we should wonder how pertinent it is to give a privileged role to unconvincing genetic bases, which imply simplifications and omissions concerning a problem that undoubtedly involves social dimensions related to the psychic suffering of children and adults in contemporary societies.

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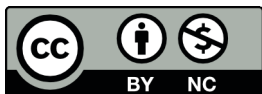
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