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Tuning major gene variants conditioning human behavior: the anachronism of ADHD

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New findings suggest that attention deficit and hyperactivity disorder (ADHD) is the most common behavioral variant associated with a mental condition. ADHD prevalence reaches figures of 18% in populations worldwide. Furthermore, genetic variants conferring susceptibility to develop ADHD are not rare but very frequent and eventually totally fixed in some populations. These patterns of evolution can be associated with the fact that this behavioral trait had provided selective advantage. However, this behavioral trait is now under scrutiny because of new emerging social necessities. Recent molecular and clinical evidence supports Thom Hartmann's Hunter–Farmer theory, reaffirming that ADHD might be an anachronic behavioral trait.

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Introduction

Behavior: a view from evolution and psychopathology and where ADHD is

Behavior can be defined as the way an organism responds to stimuli in its environment. Behavioral ecology, a branch of evolutionary biology, studies how natural selection shapes and tests animal behavior by measuring the adaptive significance and survival value (or fitness). There is no doubt that human behavior is highly implicated in conferring Darwinian advantage. In the same vein, it is a common belief that mental disorders, defined as those significant behavioral or psychological patterns associated to distress (pain), disability (functional impairment), and increased risk of suffering death, pain, disability or loss of freedom [1], are in general correlated with lower fitness. Reinforcement of this idea comes from studies performed on samples of individuals affected by schizophrenia, mood disorders, and other psychiatric conditions, in which lower fertility has been demonstrated (for review see [2,3]). In contrast with these findings, current studies performed in samples ascertained from probands affected by attention deficit and hyperactivity disorder (ADHD), the most common behavioral disorder of childhood, showed that this human behavioral condition, and some genetic variants conferring susceptibility to ADHD, displays selective advantage [4,5].

ADHD is defined as a persistent syndrome characterized by inattention, excessive motor activity, and impulsivity. ADHD affects 8–18% of children worldwide [6]. It is clear now that ADHD is not only a behavioral trait carried by American children, as suggested in the past, but a human behavioral variant that can be operatively defined in many populations worldwide [6]. Individuals with ADHD are at increased risk of poor educational achievement, low income, underemployment, legal difficulties, and impaired social relationships [7]. Annual direct costs attributable to ADHD in the United States exceeded $32 billion in 2000 [8•].

Despite the high ADHD social impact, it is unclear if ADHD should be considered as a nosological entity or as a common variant of human behavior. ADHD does occur as a single disorder in a minority of diagnosed individuals. It is generally comorbid with other behavioral and emotional conditions. The most frequent co-occurring psychiatric conditions include oppositional defiant disorder (ODD), conduct disorder (CD) and substance abuse [9••]. Furthermore, in the spectrum of behavior, as delimited by hypoactive–hyperattentive and hyperactive–inattentive subtypes, there are several clusters of behavioral subtypes — at least six — categorically different among them. These nominal categories, defined as latent classes, display different combinations of symptoms [10,11].

In this review, we focus on recent genetic and clinical advances that shape our understanding of the ADHD susceptibility as a result of genetic and evolutionary forces defining human behavior.

Defining the ADHD phenotype: categorical versus continuous

Genetic studies of ADHD typically use the categorical definitions codified in The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). Under these diagnostic systems, individuals are classified as being affected if they meet a specific number of criteria. Because of uncertainty regarding the genetic validity of DSM-IV ADHD subtypes, an alternative method of

classifying subjects, based on underlying or latent classes, has been proposed as having greater power to dissect genetically relevant ADHD subphenotypes [10,11]. Latent class analyses (LCAs) have an advantage over classical dimensional methods in that additional parameters can describe the relationship between the observed and one or more discrete unobservable variables. Additionally, rather than being based on derived factors, new classifications are obtained directly from the response items (e.g. the DSM-IV symptoms). In contrast to traditional factor analysis, factors need not be rotated to be interpretable; variables can be continuous, categorical (nominal or ordinal) or counts or any combination of these; and the normality assumption demanded by classical multivariate analyses is not required [12]. LCAs applied to parent reports of ADHD symptoms from rating scales have repeatedly yielded six to eight clusters or classes underlying the overall ADHD phenotype across several cultures, in contrast to the three fixed subtypes codified by DSM-IV ADHD [10,11]. These observed latent classes typically include the three DSM-IV defined subtypes of ADHD, but they also include classes of individuals who do not meet full DSM-IV ADHD criteria. On the whole, these findings suggest the presence of larger numbers of finely grained independent groups embedded within the ADHD phenotype than those acknowledged by current nosology. As shown in Figure 1a, at least four of the six clusters that define attention and activity (~60% of the general population) display any symptom of hyperactivity and inattention and up to ~20% of the full spectrum of ADHD. This reveals a dramatic picture of the most frequent phenotype, inattentiveness and hyperactivity, inside a social structure that rewards hypoactivity and hyperattention. LCAs also facilitate the consideration of the effects of comorbidity (Figure 1a). For example, Jain *et al.* [13], using clusters derived from the LCAs, were able to determine the presence of new regions of linkage, in addition to those described when an affection-status dichotomist trait was used. Furthermore, some regions showing nominal or suggestive linkage become very significant and sharply after using clusters that considered symptoms associated with comorbidities such as ODD, CD, alcohol abuse and nicotine dependence.

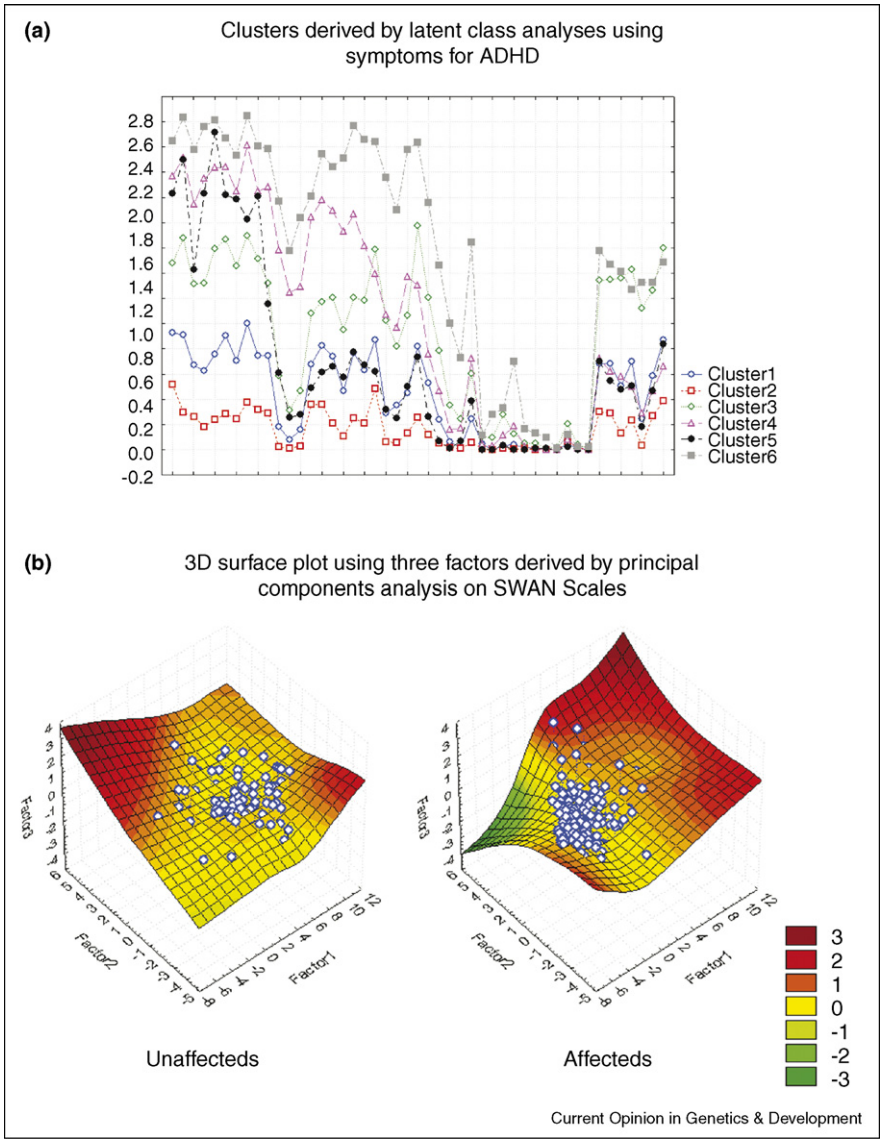
By contrast, continuous factors can be derived by extracting principal components from the list of symptoms reported by standard questionnaires used in the diagnosis of ADHD. Many authors have correlated these components with specific behavioral dimensions [14]. In addition, these extracted components enable us to discriminate among ADHD-affected and -unaffected individuals, as shown in Figure 1b. There are various particular benefits of using these 'continuous traits': the power to detect association and linkage in genetic trials is greater for continuous traits in comparison with that for categorical traits; and the specific dimensions correlated to specific behavioral symptoms (i.e. internalizing or externalizing) can be dissected from the whole picture of genetic association and linkage. As pointed out before, the problem in deriving these components or factors by standard multivariate techniques is that in a big percentage original variables do not fit normality. However, many authors have suggested that violations of normality are not fatal in the final picture.

ADHD association and linkage genetic studies: where population genetics met epidemiology

Genetic factors are strongly implicated in the etiology of ADHD. Studies in twins indicate a substantially high genetic (additive) contribution to phenotypic variation, reaching an average of 70% (for review see [15••]). Adoption studies have also confirmed that genetics rather than shared environment cause familial clustering of ADHD [16]. Family studies have confirmed the observation of increased recurrence risk by comparing the ratio of the prevalence of ADHD in various kinds of relatives to the population prevalence using the λ statistic [16]. In other words, the λ statistic is a parameter that compares 'how strong' the familial clustering of a trait is, when compared with the population prevalence [16]. These studies reported estimations of λ values for ADHD greater than 3, and these figures increased up to 20 when comorbid symptoms were included. These high λ values suggested that genes with major effects (i.e. following Mendelian laws) would govern the susceptibility to ADHD, instead of it being influenced by genes with minor effect (i.e. polygenes with indifferentiable effect size) interacting with the environment, as suggested by the multifactorial model of Falconer. In the same set of results, three independent complex segregation analyses consistently demonstrated that the model best fitting the ADHD familial data was that of a major autosomal dominant or codominant gene [16]. In addition, there is clear evidence that the presence of heterogeneity (i.e. several loci linked to the same phenotypic trait) [17], pleiotropy (i.e. a locus linked to several phenotypic traits) [13] and epistasis [18] distort Mendel proportions of segregation.

Work from several groups using candidate gene methods has led to the identification of associated pathways, primarily those metabolizing or utilizing dopamine and serotonin [16,19•,20•]. Meta-analyses applied to vast available data generated by candidate-gene approaches over dozens of genes suggest that several genes, such as *DAT*, *DBH*, *DRD1*, *DRD2*, *DRD4*, *DRD5*, 5-*HTT*, *HTR1B*, *NET1* and *SNAP25* [19•,21–23], have allelic variants that significantly change the odds of being affected by ADHD from the base level of 1.0. Furthermore, at least four groups have conducted genome-wide linkage scans for ADHD in distinct populations in an attempt to disclose novel loci that might have a large effect-size. They have reported significant linkage to 4q, 5q, 5p, 11q, 16p and 17p [13,17,24–28]. Regions located at 5p, 11q, 16p and 17p

Figure 1



A picture of the ADHD phenotype. **(a)** Six clusters derived by latent class cluster analysis using symptoms for the diagnosis of ADHD with comorbidity. Clusters 1 and 2 contain individuals that are hypoactive and hyperattentive. Clusters 4 and 6 probably correspond to the combined type, cluster 6 being more severely affected than cluster 4. Cluster 5 corresponds to the predominant inattentive type. Cluster 3 represents a mild combined group. Cluster 2, comprising 20% of individuals, represents the unique cluster unambiguously clean of behavioral symptoms associated with ADHD. The other five clusters display in some degree symptoms associated to ADHD. **(b)** Principal component analysis applied to the SWAN scale revealed three continuous factors that explain more than 90% of the variance contained in the SWAN scale. The system is able to discriminate individuals with ADHD from those that exhibit a 'normal' behavior with specificity higher than 95%. This provides a way to see a behavioral trait as a continuous phenotype instead of looking at ADHD as a categorical affected–unaffected dichotomy.

have been replicated by at least two studies [13,17,24–28]. The high degree of replication for this trait suggests that some common susceptibility genes and potentially identical variants within those genes lead to susceptibility for ADHD across populations.

In addition, Jain *et al.* [13], considering a broad ADHD phenotype that includes the presence of comorbidities, found that ADHD co-segregates with disruptive behaviors as a unique, phenotypically variable trait, as evidenced by highly significant pair-wise linkages among the following traits: ADHD and ODD (Log of odds [LOD] score = 14.19); ADHD and CD (LOD = 5.34); ODD and CD (LOD = 6.68); and CD and alcohol abuse or dependence (LOD = 3.98). This study follows these traits throughout extended pedigrees, with multiple generations, and a broad phenotype with externalizing behavioral symptoms. This comorbid ADHD phenotype

Table 1

Frequent allelic variants conferring susceptibility to ADHD.

Gene	Number of known allele variants	Susceptibility allele variant	Minimal allele frequency worldwide	Maximal allele frequency worldwide
DRD4, VNTR exon 3	9 alleles (from 2 to 11 repeats)	7R	0.01	0.78
DRD1, SNP rs4532	2 alleles (C and A)	C allele	0.03	0.50
DAT, VNTR	7alleles (10,11,12,3,7,8 and 9 repeats)	10R	0.36	1.00

Allelic frequencies reported in several populations the world over as described in ALFRED (allele frequency database), a resource of gene frequency data on human populations [30].

displayed linkage to additional loci located at 8q24, 2p21-22.3, 5p13.1-p13.3, 12p11.23-13.3, 8q15 and 14q21.1-22.2. These results were replicated using an arbitrary phenotype that was derived from latent class clusters and which also considered disruptive behavior symptoms and substance abuse or dependence [13]. Because of the significant co-segregation through many generations of ADHD and alcohol abuse or dependence demonstrated by this study, protocols looking for environmental factors must consider the possibility that maternal alcohol abuse, instead of causing ADHD, makes part of a broad phenotype that is genetically transmitted and caused by a major gene. Same consideration could be potentially relevant for nicotine abuse that is tightly comorbid with ADHD [13]. In conclusion, alcohol and tobacco abuse as well as disruptive behaviors should be considered as unique traits segregating in some affected families.

Allelic variants conferring susceptibility to ADHD are the rule and not the exception: normal is higher than 50%

The seminal paper of Ding *et al.* [4] showed that the seven-repeat (7R) allele of the human dopamine receptor D4 (*DRD4*) gene, which has been associated and linked to susceptibility to develop ADHD, is a young variant. However, the authors also demonstrated that it has been subject to advantageous selective pressure, because genetic parameters such as linkage disequilibrium (LD) extension and variability strongly deviate from the expectation provided by Kimura's neutral model of molecular evolution [29]. These results were corroborated in a second study from the same research group [5], which found a high incidence of *DRD4* 7R allele variants and a significant extensive LD around the 7R allele, suggesting positive selection [5]. Other studies performed on additional genes showed that allelic variants, conferring susceptibility to ADHD, are very frequent in the population (see Table 1). Comparing the frequency of these susceptibility variants throughout populations distributed worldwide using ALFRED (allele frequency database), a resource of gene frequency data on human populations [30], we can see the following:

1. The *DRD4* 7R variant of the variable number tandem repeats (VNTR) harbored in exon 3 shows an increase frequency as you go to South America, reaching values close to 80%.
2. The 10-repeat allele of a tandem repeat polymorphism located in the 3′ untranslated region of SLC6A3 (DAT) that is associated to ADHD susceptibility is the most frequent throughout the world, reaching fixation (gene frequency of 1.0) in some American populations.

Conclusions

In conclusion, these findings suggest overall that the ADHD phenotype represents a very common behavioral variant instead of a rare one. Furthermore, genetic variants conferring susceptibility to develop ADHD are not rare but very frequent and eventually totally fixed in some populations. These patterns of evolution can be associated with the fact that this behavioral trait had provided selective advantage (e.g. faster response to predators, best hunting performance, more effective territorial defense and improvement of capacity for mobility and settling. All these features lead to an increase in fertility and survival). However, these behavioral traits are now under scrutiny because of new emerging social necessities. As very well described by the Hunter-Farmer theory proposed by Thom Hartmann in his book 'Attention Deficit Disorder: A Different Perception', ADHD can be depicted as an important trait suited for activities like hunting and survival in a hostile environment. This trait was rewarded by natural selection over millions of years of human evolution. However, the fast revolution of human society during the past two centuries brought new challenges rewarding planning, design and attention while limiting behaviors associated to ADHD. That is what we call the anachronism of ADHD.

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