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Genetics of Attention Deficit Hyperactivity Disorder

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Abstract

ADHD is a complex neurodevelopmental disorder which cause is supposed to be a large number of genes combined with environmental factors. Main clinical symptoms are inattention, distractibility, impulsivity and hyperactivity. Data show that boys are four time more affected than girls. The diversity in presentation suggests that for more exact clinical diagnostics it is better to consider ADHD as a categorical entity, which means a continuum from normal to abnormal behavior. Family, twin and adoption studies confirmed strong hereditary factor.

The need for deeper investigation the genetic etiology and mechanisms of ADHD is enlarged with the fact that other psychiatric and behavioral disorders are commonly comorbid (especially conduct disorder, dyslexia, autism, tic disorders, depression and anxiety).

This article represents an overview on more recently published genetic studies of ADHD. Findings do not approve susceptibility genes of large effect for ADHD, but they can identify genes of smaller effect. Studies for whole genome linkage suggested some interesting results about chromosomal regions that need to be further investigated being frequently involved in the picture of this disorder.

Keywords: *genetics, ADHD, environment, comorbidity.*

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is common diagnosis in childhood and adolescence. Previously named as □minimal b
name Hyperkinetic Syndrome till in nineties in the International Classification – 10, and in the Third revision of DMS where it was named as ADHD. The most important clinical symptoms are: inattention, impulsivity, distractibility and hyperactivity. There is similarity but also some difference in the signs cited in both manuals which influence on the statistical data. Three main clinical forms are described in DMS classification: Inattentive, Hyperactive and Combined form. However, in the recent literature, the inattentive type is supposed to be a separate disorder and not only one form of ADHD.

Understanding the biological processes underlying these core symptoms leads for better diagnostics and more successful treatment of ADHD. Both genetics and environment affect genetics, ADHD, the development, trajectory and outcome of the disorder [1].

Statistics about prevalence differ depending on the used classification (ICD or DMS). However, in 2016 9,4% of children in USA are registered to suffer of ADHD. It is approved that the percentage of ADHD in different populations is as follows: in whites 9.8%, in blacks- 9.5% and in Latinos- 5.5%. Data showed that boys are four time more prone to the disorder than girls. This gender difference changes with age, but it is still present in adults aged over 19 years [2].

The follow-up of children with ADHD show that majority of these children will continue to have similar symptoms of the disorder during adulthood. Additionally, it is approved that people with ADHD are at higher risk for some functional impairments such as school inachievement, peer rejection, injuries due to accidents, they frequently manifest some criminal attitude, have occupational failure, frequently divorce, attempt to suicide, and a prematurely dye.

Imaging techniques showed that ADHD is linked mainly to dysfunction in the prefrontal cortex, basal ganglia, cerebellum, temporal and parietal cortex. Named as 'executive' these areas are important in brain activities such as response control, remembering, planning and organization activities, motivation, processing speed, but also focussing attention and control of impulsivity [3].

Even in the beginning of the diagnostic of hyperkinetic syndrome it was perceived that the disorder runs in the same families and, in this way, the possible underlying genetic component was supposed. Today, heritability estimates range is from 60 to 90%. The heritability is found to be similar in both genders and for all forms of the disorder.

Is really the ADHD genetic? The answer is difficult and complex. The exact cause of ADHD is not yet understood. However, inherited genes are undoubtedly a significant factor in the development of the disorder. Many researches confirm that genes have an important role in the aetiology of attention deficit hyperactivity disorder and its comorbidity with other psychiatric disorders. Heritability in ADHD is probably the result to a polygenic component involving many common variants each having small effects. Studies of copy number variants also showed that the rare insertions or deletions could be only some part of ADHD’s heritability [4-7].

Contemporary high technologies allow to perform many genetic studies which are just starting to link specific genes to ADHD [8]. The idea that ADHD has a hereditary component is supported by studies involved twins, all family members and adopted children. In this context, in a review of studies published ten years ago it was concluded that genetics is assumed to be the risk for the disorder in 70 to 80 percent of cases, with a mean estimate of 76 percent.

2. Methodology

This review is based on articles published more recently cited on PubMed data base. Possible risk factors especially on genetics and some environmental factors and their relationships with ADHD are discussed as well as the causality of these risks for development of the disorder. More than 4000 articles are published concerning this topic. Key words for the search were: genetics and ADHD.

In the following text some more important findings will be present, published mainly very recently, in 2019.

Epigenetic studies

It is fact that ADHD is the result of the GxE combination (gene and environment). In this context, beside to genetics, some other causes and risk factors for ADHD are supposed such as: low birth weight, brain injury, exposure to toxins during gestation, childhood exposure to lead, as well as cigarette smoking and alcohol use during pregnancy, eating too much sugar or watching a lot of TV. Unfortunately, all these factors have not strong scientific proof to be confirmed as a risk especially for ADHD [9].

Findings of Sellers et all (2019) supposed the importance of environmental factors which are involved in a sample of adopted children. The hostility of parents provoked by poor school achievement of children contribute to the continuation of ADHD symptoms and lower levels of later math ability [10]. Early intervention for preventing some symptoms are

suggested.

Genetic studies

In the very beginning of the diagnostics of ADHD, the involvement of dopamine genes has been supposed to be related to. Particularly, the D4 and D5 genes are supposed to be linked with ADHD. But the diversity and complexity of the disorder did not allow to implicate any specific gene. However, in many studies dopaminergic neurotransmission system was related to ADHD especially DRD4, DRD5, DAT1/SLC6A3, DBH, DDC. Additionally, noradrenergic system (NET1/SLC6A2, ADRA2A, ADRA2C), serotonergic system (5-HTT/SLC6A4, HTR1B, HTR2A, TPH2) but also neurotransmission and neuronal plasticity (SNAP25, CHRNA4, NMDA, BDNF, NGF, NTF3,

NTF4/5, GDNF) was mentioned to be related with ADHD development [11-16]. Some of biomarkers which are useful for ADHD diagnostics are presented on Fig. 1 [17].

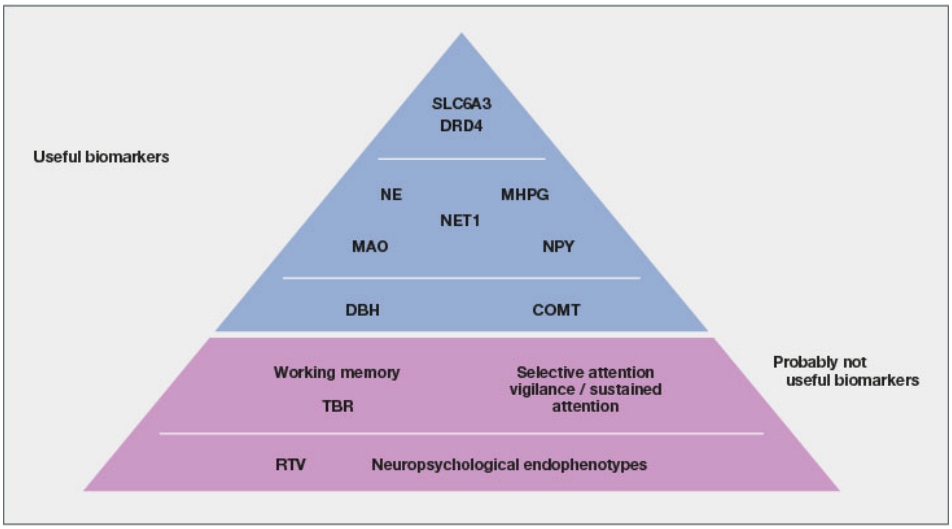

Figure 1: Possible biomarkers for ADHD diagnosis.
(Reproduced with permission from Faraone SV et al. Curr Psychiatry Res 2014; 6: 497)

In a study published in 2016 researchers discovered that ADHD children have in 41% mothers and 51% of fathers with the same diagnosis. Additionally, twin studies confirmed the hereditability in 60-80% [18]. In 2018, the study of ADHD published in Science, pointed genetic variants that are involved as a risk for ADHD in 22%. It is supposed that some of the genetic variants affect communication between brain cells, while others influence the cognitive functions, such as language and learning [19].

Further research concerned to the variations within DNA, such as duplications or deletions, and found that they are more common in individuals with ADHD (14% versus 7% in healthy children) [19, 20].

In genome-wide studies chromosome 16 is the only location which is more frequently linked with ADHD [22, 23].
Recently, in the study of Werling AM et al. (2019) it was showed that large Copy-number variants (CNVs) affect some key genes provoking many neurodevelopmental disorders like autism spectrum disorders, attention deficit hyperactivity disorder, and intellectual disability [24].
In a newest publication, genetic liability in early childhood psychopathology was named as general "p" factor, and indexed by multiple different psychiatric polygenic risk scores (PRS) evaluated in

relation with age. In this context, in schizophrenia and attention-deficit/hyperactivity disorder PRS were associated with this general "p" factor. However, PRS were not be approved for depression and autism spectrum disorder [25].

Clinical experience confirmed that ADHD is frequently comorbid with other psychiatric conditions such as bipolar disorders (BD), autistic spectrum, depression, general anxiety, obsessive-compulsive disorder, schizophrenia etc. In this context, large genome-wide association studies (GWAS) identified 19 novel ADHD risk loci and 40 novel risk loci for bipolar disorder, as well as five loci jointly associated with ADHD and bipolar disorder. Obtained results accentuate the similar genetic risk for ADHD and bipolar disorder which may help in the explanation of the high comorbidity rates but also some difficulties in differentiating between ADHD and bipolar disorder [26, 27].

A rare protein-truncating variant in evolutionarily constrained genes, was identified through exome sequences in children with ADHD and ASD in amount which are significantly higher than in controls. Consequently, a combined analysis identified microtubule-associated protein 1A (MAP1A) which is supposed to be a new exome-wide significant gene which could be the risk for psychiatric disorders in children [28, 29, 30].

The study of Waltes R. et al (2019) is aimed to explore the main effects of ASD variants and their interaction effects with environmental risk factors for ADHD. Results obtained in this study suggests that common ASD variants of the glutamatergic system (CYFIP1-rs7170637, CYFIP1-rs3693, CAMK4-rs25925, and GRM1-rs6923492) interact with psychosocial risk factors during early period of life or even prenatally, influencing the risk for ADHD common comorbidities. In this context, CYFIP1-rs3693 together with environmental interactions in early life could be the risk for ADHD diagnosis, but no significant association of any single marker is proved [31].

The development of many neurodevelopmental disorders such as intellectual disability, autism spectrum disorders, schizophrenia and ADHD could be related with some rare copy number variations (CNVs). In Icelandic and Norwegian samples eight CNVs are associate with ADHD: deletions at 2p16.3 (NRXN1), 15q11.2, 15q13.3 (BP4 & BP4.5-BP5) and 22q11.21, and duplications at 1q21.1 distal, 16p11.2 proximal, 16p13.11 and 22q11.21. However, six of the CNVs have not been associated with ADHD before (Gudmundsson et al, 2019)[32, 33] .

Genes responsible for cell adhesion are also supposed to be related with ADHD. Cell adhesion molecule 1, encoded by CADM1 gene, is a protein which facilitates cell adhesion, and is highly expressed in the human prefrontal lobe. The study of Jin J. et al, (2019) confirmed the roles of CADM1 in relation to prefrontal brain activities, inhibition function, and ADHD, indicating a potential "gene-brain-behavior" relationship of the CADM1 gene [34].

The correlation between the polymorphisms of BDNF gene (brain derived neurotrophic factor) rs11030104 and rs2030324 and executive function in children with attention deficit hyperactivity disorder was investigated by Wang N. et al (2019). Study

confirmed that ADHD children with BDNF rs2030324 GG genotype showed poor executive function which is main sign of this disorder [35].

Genetic and environmental factors is supposed to be inseparable for this complex disorder named as ADHD. However, gene expression in the brain is highly influenced by epigenetic factors. In this context, a role for DNA methylation is supposed to be important for ADHD manifestation. The study of Pineda-Cirera L. et al (2019) just confirmed the contribution of allele-specific methylation (ASM), as epigenetic mechanism that involves SNPs in correlating with differential levels of DNA methylation at CpG sites in ADHD [36].

For identifying some loci related to ADHD transcriptome-wide association study (TWAS) is used. In this context, the study conducted by Liao C. et al (2019), demonstrated that two of the previous GWAS hits can be largely explained by expression regulation. Probabilistic causal fine-mapping of TWAS signals prioritizes KAT2B in the dorsolateral prefrontal cortex and TMEM161B in the amygdala. Furthermore, two pathways (dopaminergic and norepinephrine), are supposed to be highly relevant for ADHD. Generally, these findings confirm the power of TWAS to identify and prioritize possible causal genes [37].

In a study of Sadeghiyeh T et al. (2019) the increased risk for ADHD in Iranian children is associated with the MTHFR 1298A > C polymorphism, but not with the MTHFR 677 C > T [38].

Due to different genomics discoveries it is more efficient to investigate large general child psychiatric sample and, in the following, to justify and inform their use for specific clinical purposes. In this context, in the study of Vuijk PJ. et al (2019), the logistic/linear regression and mixed effects models were used to examine associations with ADHD-related polygenic variation from the largest ADHD GWAS. ADHD polygenic risk associated with ADHD and related phenotypes as well as clinical severity was proven among child and adolescent outpatients [39].

Many researchers mentioned that ADHD in reality represents a continuum from normal to abnormal behaviour. In this context, the disorder classified as ADHD is really the extreme of a dimensional trait in the population [40]. The dimensional nature of ADHD should also explain the increases in ADHD's prevalence in recent years.

Data presented in this article are enough to show the possible genetic basis of the disorder named as ADHD. The complex interplay with environmental factors makes the diagnostics so difficult. In the future, some more and more new genetic loci together with environmental risks will discover the real cause of ADHD.

4. Conclusions

Accumulating evidence from family, twin, and molecular genetic studies suggests that ADHD represents a complex disorder caused by a combination of genetic with environmental factors.

Justification of the ADHD genetics will be challenging for any future researches. The recent technological advances enable more precise information about more genomic, transcriptomic and epigenomic data relevant to the brain structure and function.

These advances will help our understanding of the multifactor etiology of ADHD as well as our ability to precise diagnose and treatment. It is of uttermost importance, to remember that in reality, ADHD represents an extreme in the continuum from normal to abnormal behavior.

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