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Genetic and environmental background of attention deficit hyperactivity disorder (ADHD)*

Paulina Misiewicz[1, A], Joanna Iwanicka[2, B] ✉

[1] Medical University of Silesia in Katowice, Faculty of Health Sciences in Katowice, Medyków 18, 40-752 Katowice, Poland
[2] Medical University of Silesia in Katowice, Department of Biochemistry and Medical Genetics, Medyków 18, 40-752 Katowice, Poland

[A] ORCID: 0009-0001-6201-493X; [B] ORCID: 0000-0002-3609-9554

✉ jiwanicka@sum.edu.pl

ABSTRACT
Attention deficit hyperactivity disorder (ADHD) is one of the most commonly diagnosed neurodevelopmental disorders. This article aims to identify the risk factors for ADHD, with a particular focus on its genetic basis. The complex etiology of ADHD results from the interplay of both environmental and genetic factors, making it challenging to pinpoint specific determinants contributing to the disorder's phenotype. Among the most significant genetic risk factors are genes regulating the dopaminergic and serotoninergic pathways. Genetic factors involved in various biological processes, such as neuronal transmission, neural cell migration, and neurotransmitter energy metabolism, also warrant attention. Despite advancements in ADHD research, understanding the pathomechanism of this disorder remains a significant challenge for medical professionals and researchers. The limited knowledge of the biological foundations of ADHD hampers the recognition of risk variants for this disorder. Therefore, further research is necessary to identify at-risk groups and develop more effective diagnostic tests and therapeutic methods in the future.
Keywords: attention deficit hyperactivity disorder (ADHD); neurodevelopmental disorder; gene; polymorphism; risk factor; environmental factor.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is classified as a neurodevelopmental disorder by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). It is characterized by symptoms of disorganization, inattention, and hyperactivity-impulsivity, which are inappropriate for the individual's developmental level and age. In adults, these symptoms impair occupational, social, and academic functioning. In contrast, the International Classification of Diseases, 10th Revision (ICD-10) and the latest International Classification of Diseases, 11th Revision (ICD-11), used in European countries, introduce the concept of hyperkinetic disorder [1].

Attention deficit hyperactivity disorder is a prevalent condition, affecting approx. 5% of children and adolescents worldwide [2], with the prevalence in adults estimated at around 2.5% [3]. The latest meta-analysis indicates that ADHD prevalence is 7.6% in children aged 3–12 and 5.6% in adolescents aged 12–18 [4]. In the general population, ADHD is diagnosed more frequently in boys than in girls (2 : 1) and more often in men than in women (1.6 : 1). Considering the broad spectrum of ADHD symptoms, women primarily exhibit symptoms of attention deficit [5].

Family studies on the etiology of ADHD indicate that genetic factors significantly contribute to the disorder's occurrence. An analysis of 37 twin studies estimated ADHD's average heritability at 74% [6]. It is noteworthy that patients with ADHD often contend with multiple comorbidities, complicating accurate diagnosis. Therefore, proper diagnosis and individualized therapeutic approaches are crucial [7].

In this review, we summarize current knowledge regarding the genetic background of ADHD by presenting selected literature. We highlight the latest findings that contribute to understanding the etiology and pathomechanism of ADHD, as well as identifying gaps in knowledge that specify the need for further research. The literature data were reviewed using the PubMed database.

INVOLVEMENT OF ENVIRONMENTAL FACTORS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

The complex etiology of ADHD indicates that the manifestation of the phenotype depends on the interactions between genetic and environmental factors. However, it is important to note that knowledge in this area is based solely on observational studies, with no experimental research available. This lack of experimental evidence presents a challenge in definitively determining the role of environmental factors in the disorder [8].

Research has shown that low birth weight increases the risk of ADHD in children [9]. Prenatal exposure to cigarette smoke has also been identified as a predictor of the disorder. However, further research is needed to establish a causal relationship between smoking and ADHD due to the presence of confounding factors [10]. A meta-analysis suggests that alcohol consumption during pregnancy affects the occurrence

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of ADHD in children. It found that children whose mothers consumed alcohol during pregnancy had more than a two-fold increased risk of developing ADHD compared to those not exposed to alcohol in utero (OR = 2.33; 95% CI: 1.18–4.61; p = 2.0 x 10 E-02). The quantity and frequency of alcohol consumption also matter. Children whose mothers frequently and heavily consumed alcohol during pregnancy are more than twice as likely to develop ADHD than those whose mothers consumed alcohol in smaller amounts (OR = 2.28; 95% CI: 1.03–5.02; z = 2.04; p = 0.04) [11]. However, other studies did not confirm a relationship between the clinical diagnosis of ADHD in children and maternal alcohol consumption in early pregnancy [12, 13, 14], suggesting only a modest link with the occurrence of disorder symptoms in children [14].

As shown above, analyses investigating the relationship between maternal smoking and/or alcohol consumption during pregnancy and ADHD in offspring have yielded ambiguous results and require further research. The observed inconsistencies may arise from differences in ethnic backgrounds, cultural variations, and the heterogeneity of criteria for selecting study groups. Differences in the definition of dose, frequency, and timing of exposure to substances used may also be of key importance.

Another example of the connection between environmental factors and ADHD is the introduction of food additives into the diet. Consumption of artificial colorings by children increases the risk of hyperactivity. This relationship has been observed in children with hyperactivity in the general population [15].

Source data indicates that air pollution may also influence the manifestation of the ADHD phenotype. A connection has been established between the disorder and exposure to polycyclic aromatic hydrocarbons during fetal development. Studies demonstrate that these compounds disrupt the development of white matter in the left hemisphere of the brain, potentially resulting in information processing limitations, ADHD symptoms, and behavioral disorders. Additionally, postnatal exposure to polycyclic aromatic hydrocarbons can further contribute to developmental abnormalities in the dorsal prefrontal regions of white matter [16], leading to increased difficulties in information processing, behavioral deficits, and memory problems [17].

GENETIC BASIS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Research into the etiology of ADHD, including studies involving families, adopted children, and twins, indicates that specific genetic factors significantly contribute to the disorder's occurrence [6]. Attention deficit hyperactivity disorder is more common among biological parents of children diagnosed with the disorder than among adoptive parents, confirming the importance of genetic background in its etiology [18, 19]. To estimate the risk determined by genetic factors, researchers compare genetically identical monozygotic twins with genetically similar, on average, half-siblings [6].

The literature indicates a strong genetic link between extreme and subthreshold variations in ADHD symptoms. It is assumed that ADHD in the population results from the combined quantitative impact of both genetic and environmental factors, which together can determine the full spectrum of symptoms related to inattention, impulsivity, and hyperactivity [20].

INHERITANCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Based on 37 twin studies on ADHD, the average heritability of the disorder was estimated at 74% [6]. An analysis considering both genetic and environmental factors estimates this value at 88% (95% CI: 0.83–0.92). The heritability of clinically diagnosed ADHD in adults was determined to be 72% (95% CI: 0.56–0.84), while the contribution of environmental factors was relatively insignificant, estimated at 12% (95% CI: 0.08–0.17) [21].

It is worth noting that the heritability of both the inattentive and hyperactive subtypes of ADHD is comparable, at 71% and 73%, respectively. However, the significance of genetic factors differs between these subtypes. Dominant genetic effects, associated with interactions between alleles at a given locus and between different loci, are more significant in shaping the inattentive subtype compared to the hyperactive subtype. Conversely, additive genetic influences, which represent the cumulative effects of genes from multiple loci, showed the opposite results, reflecting the proportions of alleles inherited from parents [22].

Furthermore, differences in heritability estimates based on the assessment of symptoms in children with ADHD by parents and teachers have been observed. Study results demonstrate that heritability estimates made by parents and teachers are 82% and 60%, respectively. These values are higher compared to self-assessments by patients with ADHD, which estimate the heritability of the disorder at 48% [23].

MOLECULAR GENETICS OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

The goal of initial molecular research aimed at unraveling the genetic basis of ADHD was to identify genes potentially responsible for the disorder's etiology. Since the most effective treatments are based on regulating catecholaminergic transmission, these mechanisms were the focus of investigations into the genetic background of ADHD [24].

Molecular genetic studies conducted in recent years have been based on 2 hypotheses: the common disease common variant (CDCV) hypothesis and the common disease rare variant (CDRV) hypothesis. According to the CDCV hypothesis, common genetic variants, known as single nucleotide polymorphisms (SNPs), are associated with risk alleles present in more than 5% of the population. Conversely, the CDRV hypothesis posits that the development of common diseases results from the cumulative effects of multiple rare variants, specifically copy number variations (CNVs), which account for risk alleles in no more than 5% of the population [25].

CANDIDATE GENES ASSOCIATED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

Previous studies have identified numerous specific genes as potential candidates for association with ADHD. However, the limited understanding of the biological foundations of ADHD remains a constraint in accurately identifying risk variants for this disorder [26].

Potential associations of selected candidate genes with ADHD were identified based on their functions and roles in the disorder's etiology. The heterogeneity of ADHD suggests that various genetic factors may contribute to the manifestation of its phenotype. Candidate genes such as: *DAT1*, *5HTT*, *DRD4*, *DRD5*, *SNAP-25*, *ADRA2A*, *DBH*, *MAOA*, and *TPH2* provide directions for future research.

In 1 meta-analysis, the possible influence of genes related to the regulation of the dopaminergic, adrenergic, serotoninergic, and cholinergic pathways on the occurrence of ADHD was assessed. Genes involved in the development of neural structures were also considered. Among the genes of the dopaminergic pathway, *DAT1*, *DRD4*, and *DRD5* showed statistical significance. Genes related to the adrenergic and cholinergic pathways were found to be non-significant in the meta-analysis. Among genes regulating the serotoninergic pathway, *5HTT* and *5HT1B* were significantly associated with ADHD. Additionally, the *SNAP-25* gene, which influences the development of the nervous system, proved to be significant [27].

Within the *DAT1* gene, which encodes the dopamine transporter, polymorphisms significantly associated with ADHD have been identified. One of them is the 40 bp variable number of tandem repeats (VNTR) polymorphism in the 3' untranslated region (3'UTR) [28]. A significant association of this polymorphism with ADHD has been demonstrated (OR = 1.12; 95% CI: 1.00–1.27; p = 2.8 x 10 E-02). Another variant showing statistical significance with ADHD is the 30 bp VNTR, where the 3-repeat risk allele is located in intron 8 of *DAT1* (OR = 1.25; 95% CI: 0.98–1.58; p = 3.4 x 10 E-02). Additionally, a polymorphism rs27072, mapped in the 3'UTR, has shown a small but significant association with ADHD (OR = 1.20; 95% CI: 1.04–1.38; p = 6.0 x 10 E-03) [27].

Another gene potentially involved in the etiology of ADHD within the dopaminergic pathway is *DRD4*, which encodes the dopamine receptor D4. In animal models, it has been shown that this receptor plays an inhibitory role in adenylate cyclase through G protein, thereby limiting cyclic adenosine monophosphate (cAMP) accumulation [29]. Additionally, it has been confirmed that the prefrontal cortex of the brain is the primary location of *DRD4* expression, suggesting a connection between this brain region and ADHD [30]. A significant association of 2 polymorphisms within the *DRD4* gene with this disorder has been confirmed. The first is a 48 bp VNTR located in exon 3. The 7-repeat allele demonstrated statistical significance (OR = 1.33; 95% CI: 1.15–1.54; p = 7.0 x 10 E-05). The second polymorphism is rs1800955, mapped 521 bp upstream of the transcription start site. A significant association has been observed between carrying the T allele of this polymorphism and ADHD compared to the C allele (OR = 1.21; 95% CI: 1.04–1.41; p = 7.0 x 10 E-03) [27].

The literature also highlights the significance of the dopamine receptor D5, part of the D1-like receptor family, which is responsible for activating adenylate cyclase and leading to the accumulation of cAMP [31]. The *DRD5* gene, encoding this receptor, is highly expressed in the hippocampus [32]. Notably, a statistically significant association was found with the 18.5 kb dinucleotide located in the 5' flanking region [33]. A meta-analysis revealed an association of the 148-bp allele with ADHD (OR = 1.23; 95% CI: 1.06–1.43; p = 2.7 x 10 E-03) [27].

Genes involved in regulating the serotonin pathway may also play a significant role in the complex etiology of ADHD. The *5HTT* gene, located on chromosome 17, is particularly noteworthy [34]. The protein encoded by this gene is responsible for the reuptake of serotonin in the synaptic space [35]. The brain region with the highest density of serotonin transporter binding complexes is the raphe nuclei [36], with the dorsal raphe nucleus being associated with the development of depression [37]. Other regions associated with this neurotransmitter include the basal ganglia and cortical areas [36]. Research indicates reduced basal ganglia volume and decreased activation in individuals with ADHD [38], supporting the link between this gene and ADHD. An association has been found between ADHD and the long allele resulting from the insertion of a 40 bp sequence in the promoter region of the *5HTTLPR* gene (OR = 1.17; 95% CI: 1.02–1.33; p = 1.0 x 10 E-02) [27].

The regulation of the serotonin pathway also involves the *5HT1B* gene located at locus 6q13 [39]. It encodes the serotonin receptor 1B (5HT1B), which is coupled with a G protein that inhibits cAMP synthesis [40]. The primary site of *5HT1B* gene *(HTR1b)* expression is the anterior cingulate cortex [41], a region noted for its importance in the context of social exclusion experiences [42]. A statistically significant association regarding ADHD has been demonstrated for the carrier status of the G allele of the rs6296 polymorphism located in exon 1 of this gene (OR = 1.11; 95% CI: 1.02–1.20; p = 1.0 x 10 E-02) [27].

To better understand the genetic basis of ADHD, genes whose protein products are involved in nervous system development have also been analyzed. One such gene is *SNAP-25*, located at locus 20p11.2. The protein encoded by this gene is associated with synaptic connection plasticity and axonal growth. It also plays a role in the docking and fusing of vesicles within presynaptic neurons [43]. Meta-analysis results showed that the T allele of the rs3746544 polymorphism located in the 3'UTR region increases the risk of ADHD by 15% (OR = 1.15; 95% CI: 1.01–1.31; p = 3.0 x 10-02) [27].

GENOME-WIDE ASSOCIATION STUDIES

Genome-wide association studies (GWAS) have identified 12 new loci that may predispose individuals to ADHD. Among these, the strongest association with ADHD has been attributed to the polymorphic variant rs11420276 (OR = 1.11; p = 2.14 x 10 E-13), located on chromosome 1 within the non-coding sequence of the *ST3GAL3* gene [44]. Literature data also indicate a link between missense mutations in *ST3GAL3* and intellectual disability [45]. Additionally, the rs11210892 polymorphism in the same locus

has been associated with schizophrenia [46], a condition often accompanied by ADHD symptoms [47]. Studies using the fruit fly *Drosophila melanogaster* further support the hypothesis regarding the association of *ST3GAL3* with ADHD [48].

Another gene identified in the region associated with ADHD is *FOXP2*, located on chromosome 7 [44]. Its product, the forkhead box protein P2 (FOXP2), serves as a transcription factor. This gene plays an important role in neural connections [49] and is linked to the neuronal mechanisms of speech and learning development [50]. Research confirms a connection between the disruption of these processes and the development of ADHD [47]. The rs5886709 polymorphism of *FOXP2* showed a statistically significant association with ADHD (OR = 1.08; p = 1.66 x 10 E-08) [44]. Another analysis highlights the significance of *FOXP2* in adult ADHD, showing that the rs12533005 polymorphism increases the risk of the mixed subtype of the disorder by 30% (OR = 1.30; 95% CI: 1.09–1.56; p = 3.3 x 10 E-03) [51].

Another gene whose SNPs may predispose to ADHD is *SORCS3*, located on chromosome 10 [44]. This gene encodes a transmembrane brain receptor that plays a significant role in synaptic activity in neurons [52]. Meta-analysis results indicate the significance of the rs11591402 *SORCS3* polymorphism (OR = 0.91; p = 1.34 x 10 E-08) as a protective factor against ADHD [44]. Additionally, the literature suggests a link between *SORCS3* and various mental disorders, including: ADHD, autism spectrum disorders, depression, bipolar affective disorder, and schizophrenia [53].

Genes *LINC0046* and *TMEM161B*, located on chromosome 5, are also noteworthy. The associated rs4916723 polymorphism may have a protective role against ADHD (OR = 0.93; p = 1.58 x 10 E-08) [44]. The *LINC00461* gene may play a significant role in shaping the risk of developing psychiatric disorders such as: depression, schizophrenia, bipolar affective disorder, and ADHD. Research also suggests its association with neuroticism and anxiety disorders. Analyses in animal models suggest a probable role for this gene in regulating the movement of nerve cells during prenatal development [54]. On the other hand, the *TMEM161B* gene is associated with the amygdala [55], the volume of which may be reduced in individuals with ADHD. Dysfunction of the amygdala in this group of patients results in reduced impulse control and poorer emotion processing [56].

Another polymorphism potentially related to ADHD is rs1427829, located within the *DUSP6* gene on chromosome 12 (OR = 1.08; p = 1.82 x 10 E-09) [44]. The gene's product is a dual-specificity phosphatase [57], which plays a role in maintaining the homeostasis of dopamine transporters [44].

The *SEMA6D* gene, mapped to chromosome 15, is active in the brain, kidneys, and placenta during embryonic development and is also expressed in the brains and kidneys of adults. Studies in animal models have shown that the products of *SEMA6D* inhibit nerve cell development and may play an important role in the functioning and regeneration of the nervous system, particularly in adult tissues [58]. Meta-analysis results indicate the significance of the rs281324 *SEMA6D* polymorphism (OR = 0.93; p = 2.68 x 10 E-08) as a protective factor against ADHD [44].

The latest GWAS have revealed that among the analyzed SNPs, the rs6686722 TNR variant shows the strongest association with ADHD (p = 3.15 x 10 E-08). This polymorphism is located 22.8 kbp upstream of the *TNR* sequence [26]. The *TNR* gene encodes tenascin R, a glycoprotein in the extracellular matrix of nervous system cells. Literature indicates the importance of tenascin R in processes such as neuronal adhesion, differentiation, and modulation of nerve fiber growth. Additionally, *TNR*, in conjunction with fibronectin, inhibits neurite growth and cell adhesion, affecting synaptic connections [59]. It is believed that the weakening of synapses and dendritic atrophy are associated with disturbances in cognitive function, perception, and emotional expression, potentially leading to psychiatric and neurodegenerative disorders [60].

Another SNP showing an association with ADHD is rs2410116 (OR = 0.50; 95% CI: 0.38–0.65; p = 4.06 x 10 E-07), located on chromosome 8. This variant, situated within a gene desert 300.2 kbp upstream of the *DLC1* gene, may have a protective function against ADHD symptoms [26]. Literature also indicates an association between the rs289519 *DLC1* polymorphism and nicotine dependence in the African American population (p = 4.45 x 10 E-08) [61]. This is relevant in light of clinical studies suggesting a genetic link between nicotine addiction and ADHD. Individuals with ADHD are more likely to start smoking at younger ages and progress to regular smoking more quickly. Moreover, smokers with ADHD report more intense withdrawal and craving during abstinence than non-ADHD smokers [62]. Additionally, the VNTR polymorphism within the *DRD4* gene is associated with nicotine craving [63], while the 9-repeat allele of the *DAT1* gene polymorphism is considered a protective factor against smoking addiction among young adults [64].

It should be emphasized that while the source data identify these genes as candidates for association with ADHD, they also suggest possible implications of a genetic basis for nicotine addiction linked with ADHD [65].

The *SPATA7* gene, located on chromosome 14, also appears significant in the context of ADHD predisposition. This gene is expressed in various tissues, including the retina of the eye [66]. One characteristic of ADHD is impaired information processing time [67]. Whole-genome study results confirm an association between DNA variability in the *SPATA7* sequence and reaction times in patients (p = 2.71 x 10 E-06) [68]. Current literature suggests a protective role for the rs61975260 *SPATA7* polymorphism against ADHD (OR = 0.49; 95% CI: 0.37–0.65; p = 5.97 x 10 E-07) [26].

Another polymorphism that may predispose to ADHD is rs77224013 (OR = 3.87; 95% CI: 2.25–6.65; p = 9.64 x 10 E-07). It is mapped to chromosome 21, 58.4 kbp upstream of the gene encoding the subunit of interferon alpha and beta receptor (*IFNAR2*) and 94.8 kbp upstream of the gene encoding the beta subunit of interleukin 10 receptor (*IL10RB*). In this region, other immune-related genes, such as *IFNAR1*, are also located [26]. Additionally, children with ADHD have been observed to have higher levels of interleukin 6 compared to healthy peers [69]. Immune system imbalances are considered potential risk factors for ADHD among individuals with genetic predispositions [70].

Studies have shown that children with ADHD have an increased frequency of brain developmental abnormalities, possibly due to the disruptive impact of heterotopic neuronal migration [71]. Furthermore, a 5% reduction in total cortical volume has been observed in individuals with ADHD compared to the control group, with this difference persisting throughout development. Local differences indicate that this reduction occurs in several cortical areas, particularly in the frontal lobes. Data also confirm reductions in cortical surface area and the formation of cortical convolutions and gyri [72]. However, determining the common basis for brain structural abnormalities and increased cytokine production requires further research.

In addition to the aforementioned genomic variants, the results of the whole-genome association study indicate 108 other SNPs showing an association with ADHD (ranging from $p \leq 9.91 \times 10$ E-05 to 1.01×10 E-06). It is important to note that the GWAS was conducted on a relatively small group of individuals, which is associated with lower statistical power of the obtained relationships and represents a limitation of the applied methodology [26].

Single nucleotide polymorphism-genome-wide association studies (SNP-GWAS) and copy number variation-genome-wide association studies (CNV-GWAS)

Genome-wide association studies investigating familial associations of genetic variants with ADHD have identified significant links between the disorder and the cadherin 13 (*CDH13*) and glucose-fructose oxidoreductase 1 (*GFOD1*) genes. In the non-coding sequence of the *CDH13*, rs6565113 emerged as statistically significant ($p = 5.0 \times 10$ E-03), and within the intron of the *GFOD1* gene, significance was found for rs552655 ($p = 4.0 \times 10$ E-03). The rs6565113 variant is most strongly associated with excessive talkativeness, while rs552655 is linked to losing objects. Both polymorphisms have also been associated with difficulties in sustaining attention [73]. *CDH13* is involved in the negative regulation of neuronal growth, and a high distribution of cadherin 13 has been confirmed, indicating its probable role in neuronal circuitry [74]. On the other hand, the *GFOD1* gene encodes a protein presumably involved in metabolic processes and electron transport-related functions, but its specific role in the etiology of ADHD has not been fully elucidated [75].

Based on 37 twin studies, the heritability of ADHD has been estimated at 74% [6]. However, SNP analyses estimate the heritability of the disorder at 22%. Discrepancies in results suggest that the major genetic determinants of ADHD may be associated with very rarely occurring SNP alleles or sets of more common polymorphisms, each having a small phenotypic effect, which impacts the statistical power of the studies [76].

Among rare variants related to the complex genetic architecture of ADHD, CNVs stand out. Copy number variations are deletions or duplications encompassing coding or non-coding segments of genetic material and can involve up to 10% of the human genome. They are prevalent among ADHD patients but occur with varying frequencies [76]. Literature data confirm the association of both rare and common variants with ADHD. Polymorphism rs12842 (OR = 1.57; $p = 6.0 \times 10$ E-04) and the duplication of *SLC2A3* (OR = 1.76; 95% CI: 1.12–2.77; $p = 1.5 \times 10$ E-02) are associated with cognitive processing and may lead to neurocognitive deficits. However, the association with ADHD for the polymorphic variant was demonstrated in a cohort spanning several European countries, while the duplication was population-specific and reached statistical significance only in the German cohort [77].

WHOLE EXOME SEQUENCING

Whole exome sequencing (WES) has been used to identify genes associated with Mendelian disorders that share phenotypic features with ADHD, such as inattention and hyperactivity. A total of 139 candidate genes contributing to 137 disorders characterized by at least 1 ADHD symptom were identified. These genes are involved in nicotine dependence, forebrain maturation, cognitive processes, and the formation of synaptic spaces. They also play roles in metabolic processes and glutaminergic transmission, mechanisms characteristic of ADHD.

Rare gene variants, specifically *WAC*, *KIF11*, and *CRBN*, were shown to be associated with the severity of attention deficit symptoms, though this was not confirmed for hyperactivity and impulsivity traits. Within the *WAC* gene, a statistically significant polymorphism, rs201855730 ($p = 1.03 \times 10$ E-04), was identified. The study also revealed significance for the variant 10:92613567–A in *KIF11* ($p = 4.81 \times 10$ E-06). In the case of the *CRBN* gene, attention is drawn to 3 variants potentially linked to ADHD: 3:3150954–G, 3:3174156–T, and rs201449042 ($p = 3.03 \times 10$ E-06) [78]. These genes are involved in the pathomechanism of disorders that include clinical symptoms of ADHD. *WAC* gene mutation is responsible for Desanto–Shinawi syndrome, which includes behavioral disorders and developmental delay [79]. *KIF11* has been associated with lymphatic edema, microcephaly, and intellectual disability [80]. There is also a suggestion of a connection between *CRBN* mutations and developmental delay through gene copy number increases [81].

The analysis of common variants led to the identification of 6 genes associated with ADHD. Five of them were linked to hyperactivity: *UQCC2*, *MANBA*, *FOXP1*, *KANSL1*, and *HIVEP2*, with the latter 2 also attributed to impulsivity traits. The *MANBA* gene is also involved in psychiatric disorders and has been linked to the development of schizophrenia and nicotine addiction [82]. In this analysis, *MANBA* showed the highest statistical significance with ADHD ($p = 5.99 \times 10$ E-08) [78].

The genes *FOXP1*, *HIVEP2*, and *KANSL1* exhibited statistical significance with ADHD at levels of $p = 2.43 \times 10$ E-03, $p = 1.10 \times 10$ E-03, and $p = 3.56 \times 10$ E-03, respectively. Previous studies have indicated a connection between *HIVEP2* and *FOXP1* and autism spectrum disorders [83, 84, 85]. Furthermore, *HIVEP2* has been linked to anxiety, while *FOXP1* has been associated with aggression. These 3 genes are of particular interest to researchers due to their presumed pleiotropic role in the context of ADHD and associated comorbidities [78].

Finally, the latest meta-analysis of a GWAS on ADHD identified 27 significant loci, with the *PPP1R16A* and *B4GALT2* genes being the most significant. It was estimated that 84–98% of variants influencing ADHD are shared with other psychiatric disorders. Furthermore, common-variant ADHD risk was associated with

complex cognitive function disorders, such as verbal reasoning and several executive functions, including attention [86].

NETWORK ANALYSIS AND FUNCTIONAL CHARACTERISTICS OF GENES ASSOCIATED WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

A literature review suggests that the etiology of ADHD is most likely based on a polygenic concept, positing that the disorder results from the contributions of multiple risk genes with moderate effects. These candidate genetic variants are distributed throughout the entire genome, and their precise localization is typically determined using functional enrichment analysis. This approach allows for a broader assessment encompassing the entire biological pathway of a given gene, thereby facilitating the identification of new risk variants.

Network analysis aims to identify new genes that interact with or form network connections with genes predisposing to ADHD [25]. One such analysis revealed that ADHD is associated with the overexpression of genes involved in specific biological processes, including neuronal signaling, neuronal movement, the energetic metabolism of neurotransmitters, and processes involving G-proteins. It is notable that some of these genes are associated with genetic variants linked to ADHD in whole-genome analysis [87].

In recent years, significant progress has been made in research aimed at determining the genetic determinants of ADHD. However, this research has not yet provided exhaustive information about the pathomechanism and potential functional significance of identified genetic variants [25].

CONCLUSIONS

According to the current state of knowledge, the genetic aspect plays a significant role in shaping the risk of ADHD. The polygenic nature of the disorder means that genes regulating dopaminergic and serotonergic pathways, as well as those involved in numerous biological processes, contribute to its etiology. The contribution of environmental factors is also important. Consequently, genetic testing appears promising for predicting treatment response, drug tolerance, and identifying risk groups. However, the usefulness of current genetic data in everyday clinical practice still has many limitations. It should be emphasized that the identified genetic factors refer to candidate genes and may modify the risk of ADHD without causally translating into the phenotype. Therefore, further research in this area is needed to better understand the pathomechanism of ADHD and to develop more effective diagnostic and therapeutic methods.

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