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Genetics and Neuroscience Biomarkers in Attention-deficit/hyperactivity disorder: Insights toward Precision Medicine, A Systematic Review

Ronak Mesroghli[1], Seyed Mahmoud Tabatabaei[2]

1. Department of Psychology, Tabriz Branch, Islamic Azad University, Tabriz, Iran
2. Department of Medical Physiology, TaMS.C., Islamic Azad University, Tabriz, Iran

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Abstract

Background & Objectives: Attention-deficit/hyperactivity disorder (ADHD) affects approximately 5 to 7% of children and 2 to 5% of adults worldwide, with heritability estimates of 70 to 80% reported in recent genome-wide association studies (GWAS) (1). The disorder arises from complex interactions among genetic, neurobiological, and environmental factors. This systematic review synthesizes recent advances in genetic and neuroscience-based biomarkers and evaluates their potential utility for precision medicine approaches in ADHD.

Materials & Methods: Study quality was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool and the Newcastle–Ottawa Scale. A systematic review of the literature published up to October 2025 was conducted, encompassing GWAS, neuroimaging studies (functional magnetic resonance imaging and electroencephalography), and clinical trials. The analysis focused on key genetic variants involved in dopamine regulation, including dopamine receptor D4 (DRD4), dopamine transporter 1 (DAT1), and catechol-O-methyltransferase (COMT), neurophysiological markers such as the theta-to-beta ratio, and polygenic risk scores (PRS) for treatment response prediction. Data were retrieved from PubMed and Scopus databases.

Results: Genetic variants affecting dopaminergic signaling were associated with increased ADHD susceptibility and differential responses to stimulant medications. The incorporation of PRS improved the prediction of treatment response by increasing explained variance, for example, R^2 values rose from 0.05 to 0.28, representing an absolute increase of approximately 23%, although relative improvements varied between 15 and 25% across studies. Electroencephalography-based neurofeedback demonstrated small-to-moderate improvements in executive functioning among inattentive ADHD subtypes, with standardized mean differences ranging from 0.36 to 0.44, although ongoing debates suggest that a substantial proportion of observed effects may reflect placebo-related mechanisms (I^2 = 50 to 65%). Neuroimaging findings consistently revealed hypoactivation of the prefrontal cortex and dysconnectivity within the default mode network, facilitating subtype differentiation. Integrative approaches employing artificial intelligence showed promise for individualized treatment planning; however, financial constraints, limited accessibility, and methodological heterogeneity currently hinder widespread clinical implementation.

Conclusion: Genetic and neurobiological biomarkers provide a robust foundation for precision-oriented ADHD care, encompassing neurofeedback and pharmacogenomic strategies. Standardization of biomarker assessment tools and the strategic integration of artificial intelligence are essential to overcoming existing barriers and promoting equitable, outcome-optimized interventions.

Keywords: Attention Deficit Disorder with Hyperactivity, Genetic Markers, Precision Medicine, Neurofeedback, Electroencephalography

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Corresponding Author: Ronak Mesroghli, Department of Psychology, Tabriz Branch, Islamic Azad University, Tabriz, Iran.
Email: ronakmesroghli@gmail.com

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent neurodevelopmental disorders, affecting

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approximately 5 to 7% of children and 2.5 to 6% of adults worldwide (1). In Iran, recent meta-analyses estimate the prevalence among school-aged children to be approximately 8 to 11% (2). ADHD is characterized by persistent patterns of inattention, hyperactivity, and impulsivity, which substantially impair academic achievement, social functioning, and overall quality of life (3). The disorder constitutes a complex and heterogeneous condition shaped by the interplay of genetic, neurobiological, and environmental influences (4).

The etiology of ADHD encompasses multiple contributing mechanisms, including genetic vulnerability, neurotransmitter dysregulation, and structural as well as functional brain alterations. Twin studies consistently demonstrate a strong hereditary component, with heritability estimates ranging from 70 to 80% (5). Several genetic polymorphisms, particularly within dopamine-related genes such as DRD4 (dopamine receptor D4), DAT1 (dopamine transporter 1), and COMT (catechol-O-methyltransferase), have been robustly implicated in ADHD pathophysiology (6, 7). In parallel, neuroimaging studies have identified abnormalities in the prefrontal cortex, basal ganglia, and cerebellum, thereby reinforcing the neurobiological basis of the disorder (8, 9).

Although pharmacological treatments, including stimulant medications such as methylphenidate, and evidence-based behavioral therapies are widely implemented, treatment response remains highly variable across individuals. As discussed in Section 2.1 and summarized in Table 1, up to 20 to 30% of patients exhibit inadequate therapeutic outcomes (10). This variability underscores the necessity of adopting a precision medicine framework, in which interventions are tailored to individual biological and clinical profiles (11). Precision-based approaches integrate genetic, neurophysiological, and biochemical biomarkers to guide treatment selection, optimize therapeutic efficacy, and minimize adverse effects (12).

Accumulating evidence indicates that polymorphisms in neurotransmitter-related genes, including DRD4, DAT1, COMT, and APOE4, influence both ADHD susceptibility and responsiveness to treatment (7, 13). Complementary neurophysiological markers, such as electroencephalographic patterns,

Table 1. Comparison of Treatment Modalities for ADHD.

Treatment Modality	Effectiveness on Core Symptoms	Side Effects/ Limitations	Strengths/Benefits	References
Stimulant Medications (e.g., Methylphenidate)	High effectiveness in reducing inattention and hyperactivity	Insomnia, appetite suppression, increased anxiety	Widely used, well-researched	19, 24, 25
Non-stimulant medications (e.g., Atomoxetine)	Moderate effectiveness, particularly in inattentiveness	Fatigue, stomach upset, possible liver issues	Suitable for patients intolerant to stimulants	20, 23
Cognitive Behavioral Therapy (CBT)	Moderate improvements in executive function and behavior (SMD=0.4-0.6)	Minimal, e.g., no pharmacological risks	No side effects; addresses underlying cognitive deficits through skill-building	21, 28
Neurofeedback	Small-to-moderate (debated; SMD=0.2-0.4) for improving attention and behavior regulation	Requires significant clinician expertise, not standardized protocols	Non-invasive focuses on brainwave activity	29, 31
Combined Approaches (e.g., Medications + CBT/Neurofeedback)	High effectiveness for multifaceted ADHD symptoms	Requires multi-modal treatment planning	Addresses multiple facets of ADHD simultaneously	22, 30

and biochemical indicators derived from peripheral assays provide additional insights into underlying pathophysiological processes (14, 15). Collectively, these advances establish a foundation for targeted, mechanism-driven interventions that address the core neurobiological substrates of ADHD (16).

This systematic review integrates findings from genetic, neuroimaging, and neurophysiological research to clarify the role of biomarkers in ADHD management. By synthesizing evidence across these domains, we demonstrate how biomarker-informed strategies can enhance diagnostic precision, predict therapeutic responsiveness, reduce treatment-related adverse effects, and improve long-term outcomes. Ultimately, this review advocates for the implementation of a precision medicine paradigm that aligns interventions with individuals' distinct biological signatures, thereby promoting optimized and equitable care for patients with ADHD (17, 18).

Despite significant advances in pharmacological and behavioral treatments, inter-individual variability in therapeutic response, driven by genetic heterogeneity, neurobiological diversity, and environmental influences, remains a major clinical challenge, with up to 30% of patients experiencing insufficient benefit (10, 11). Current clinical practice frequently relies on empirical trial-and-error approaches, often neglecting biomarker-guided personalization that could maximize efficacy while reducing side effects. This systematic review addresses this gap by synthesizing evidence from genetic analyses, neuroimaging, and neurophysiological investigations to delineate biomarker-based strategies for precision medicine in ADHD, with the goal of improving diagnostic accuracy, predicting treatment response, and supporting equitable clinical interventions.

ADHD and Current Treatment Challenges

The contemporary treatment landscape for ADHD encompasses both pharmacological and non-pharmacological approaches, reflecting the disorder's multifactorial neurobiology involving dopaminergic and noradrenergic dysregulation within prefrontal–striatal circuits. First-line pharmacological treatments include stimulant medications, such as methylphenidate and amphetamines, which enhance synaptic dopamine and norepinephrine availability to improve executive functioning and inhibitory control. Non-stimulant agents, including atomoxetine and guanfacine, target norepinephrine reuptake mechanisms or alpha-2 adrenergic receptors, respectively (19, 20). Non-pharmacological interventions, such as cognitive behavioral therapy, parent-training programs, and school-based strategies, complement pharmacotherapy by promoting adaptive behavioral skills and supportive environmental structures for affected individuals and their families (21, 22).

Limitations of Current Treatments

Despite their demonstrated efficacy, existing interventions are associated with notable neurobiological and practical limitations, reflecting the inherent complexity of ADHD at both circuit-level and molecular scales.

Pharmacological Limitations:

• **Variable Efficacy:** Approximately 20 to 30% of individuals exhibit suboptimal responses to stimulant medications, often attributable to genetic polymorphisms and, in some cases, comorbid neuroinflammatory processes (19, 23).

• **Adverse Effects:** Common side effects include insomnia, appetite suppression, and increased anxiety, which may exacerbate prefrontal cortical hypoactivation in vulnerable neural circuits (24, 25).

• **Incomplete Symptom Coverage:** Although attentional deficits often improve, symptoms of hyperactivity, impulsivity, and oppositional behavior may persist, suggesting incomplete modulation of basal ganglia–cerebellar networks (22, 26).

• **Long-Term Risks:** Prolonged stimulant

exposure has raised concerns, primarily from animal studies, regarding potential cardiovascular risks and subtle alterations in neuroplasticity, although robust human data remain limited (24, 27).

Non-Pharmacological Limitations:

• **Resource Intensity:** Behavioral interventions require sustained involvement from caregivers, educators, and clinicians, thereby limiting scalability, particularly in resource-limited settings (28).

Response Heterogeneity

Treatment outcomes vary considerably among individuals with ADHD, with some patients demonstrating substantial improvement and others showing minimal benefit. This heterogeneity highlights the urgent need for neurobiologically informed patient stratification (21, 29). Although neurofeedback interventions show emerging promise, their specificity remains debated, as several meta-analyses suggest that observed benefits are modest and may be largely attributable to non-specific therapeutic effects rather than targeted neurophysiological modulation.

Table 1 summarizes the comparative effectiveness, limitations, and strengths of current pharmacological and non-pharmacological interventions for ADHD, thereby providing a concise overview of how each therapeutic modality addresses core symptom domains.

The Imperative for Personalized Medicine in ADHD

The neurobiological heterogeneity of ADHD, encompassing genetic susceptibility, circuit-level dysconnectivity, and environmental modulators, substantially amplifies inter-individual variability in treatment response, thereby necessitating the adoption of a precision neuroscience paradigm. This framework integrates the following components:

• **Genetic Markers:** Polymorphisms in dopamine-related genes, including DRD4, DAT1, COMT, and Apolipoprotein E (APOE4), particularly in relation to cognitive outcomes in comorbid presentations, predict differential pharmacodynamic responses. These markers enable genotype-guided dosing strategies aimed at optimizing prefrontal dopaminergic signaling (30, 31).

• **Biomarkers:** Multimodal assessment tools, such as electroencephalography-derived theta-to-beta ratios, functional magnetic resonance imaging indices of prefrontal activation, and peripheral biochemical assays, including inflammatory cytokines, provide objective prognostic indicators of treatment efficacy and tolerability (32, 33).

• **Tailored Interventions:** The integration of genetic and biomarker profiles reduces reliance on empirical trial-and-error approaches and promotes circuit-specific therapeutic strategies that minimize non-response rates and adverse events (33).

Biomarker-centric models hold transformative potential for ADHD therapeutics by refining clinical outcomes across inattentive, hyperactive, and comorbid phenotypes, while also addressing residual symptoms that remain refractory to conventional treatment approaches. Subsequent sections systematically delineate recent advances in genetic and biomarker research, elucidating their role in the development of individualized treatment regimens. Collectively, these challenges underscore the necessity of a comprehensive synthesis of biomarker evidence, as presented in the following Methods and Results sections.

Materials and Methods

Protocol and Registration

This systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological rigor, transparency, and reproducibility. The review protocol was prospectively registered and publicly archived on Zenodo under the Digital Object Identifier 10.5281/zenodo.17688415 prior to data extraction

and synthesis. The registered protocol specifies the study objectives, comprehensive search strategy, inclusion and exclusion criteria, and planned analytical procedures, thereby ensuring transparency and methodological consistency.

Eligibility Criteria

Eligible studies were selected using the PICO framework, defined as follows: Population, individuals diagnosed with ADHD; Intervention, genetic, neurophysiological, or biochemical biomarkers; Comparison, standard treatments, active comparators, or placebo or no-treatment controls; and Outcomes, diagnostic accuracy, treatment efficacy, or symptom modulation. Inclusion criteria comprised: (1) peer-reviewed studies published in English up to October 2025, acknowledging that the English-only restriction may introduce language bias; (2) genome-wide association studies, neuroimaging investigations (functional magnetic resonance imaging or electroencephalography), or clinical trials examining dopamine-related genes, including DRD4, DAT1, and COMT, neurofeedback interventions, or biochemical markers; and (3) pediatric or adult populations with a formal diagnosis of ADHD. Exclusion criteria included non-English publications, studies published prior to 2000, case reports, and investigations lacking genetic or biomarker-related data.

Information Sources

Systematic literature searches were conducted across PubMed, Scopus, Web of Science, and Google Scholar, with reproducible keyword limits and rigorous duplicate removal procedures implemented to ensure replicability. The search period spanned January 2000 to October 2025, capturing contemporary developments in ADHD biomarker research.

Search Strategy

A comprehensive search strategy incorporating Medical Subject Headings and free-text terms was developed as follows: (“ADHD” OR “attention-deficit/hyperactivity disorder”) AND (“genetics” OR “biomarkers” OR “neurofeedback” OR “neuroimaging” OR “ Electroencephalography (EEG)” OR “fMRI” OR “dopamine” OR “DRD4” OR “DAT1” OR “COMT” OR “polygenic risk score” OR “theta/beta ratio” OR “PRS”). Boolean operators and truncation techniques were applied to maximize sensitivity and specificity. The full PubMed search string is reported below: ((“ADHD”[MeSH Terms] OR “Attention Deficit Disorder with Hyperactivity”[MeSH Terms] OR “attention-deficit/hyperactivity disorder” OR “ADHD”) AND (“Genetics”[MeSH Terms] OR “genetic markers” OR “biomarkers”[MeSH Terms] OR “neurofeedback” OR “neuroimaging”[MeSH Terms] OR “EEG” OR “fMRI” OR “dopamine”[MeSH Terms] OR “DRD4” OR “DAT1” OR “COMT” OR “polygenic risk score” OR “theta/beta ratio”)) AND (“2000/01/01”[Date - Publication] : “2025/10/31”[Date - Publication]). Searches were independently conducted by two reviewers (R.M. and S.M.T.) to minimize selection bias.

Selection Process

Study selection proceeded in two sequential stages: initial screening of titles and abstracts for relevance, followed by full-text evaluation against predefined eligibility criteria. Discrepancies were resolved through consensus or, when necessary, consultation with a third reviewer. The PRISMA flow diagram (Figure 1), presented in the Results section, illustrates the selection process, wherein 300 records were identified, 150 were screened after duplicate removal, 77 full texts were assessed for eligibility, and 73 were excluded due to insufficient data or failure to meet inclusion criteria.

Data Collection Process

Data extraction was independently performed by two reviewers using a standardized data collection form, which was piloted on ten studies to ensure consistency and reliability. Extracted variables included study design, participant characteristics (age, sex, ADHD subtype), biomarker category (genetic, neurophysiological, biochemical), outcome measures, and reported effect sizes.

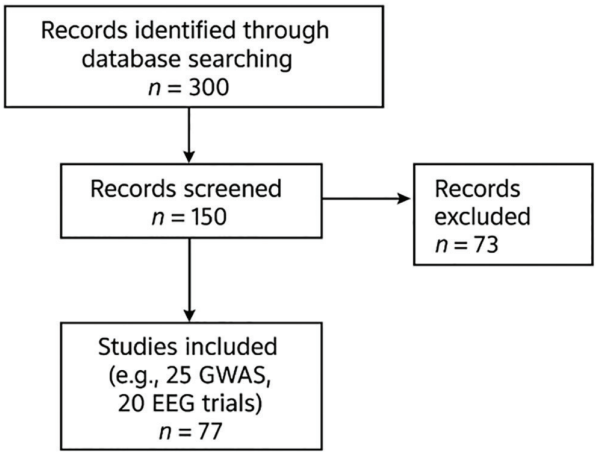


Figure 1. PRISMA flow diagram of study selection process. (Records identified through database searching n=300; screened n=150; excluded n=73; included n=77, including 25 GWAS and 20 EEG trials).

Discrepancies were resolved through discussion, and corresponding authors were contacted to obtain missing data when required.

Data Items

Primary outcomes comprised: (1) diagnostic accuracy of biomarkers, such as theta-to-beta ratios and default mode network connectivity; (2) treatment efficacy, including stimulant response rates and neurofeedback effect sizes; and (3) predictive validity of genetic markers, such as the DRD4 seven-repeat allele and polygenic risk scores. Secondary outcomes included adverse effects and long-term clinical outcomes.

Risk of Bias in Individual Studies

Methodological quality was evaluated using the Cochrane Risk of Bias 2 tool for randomized controlled trials and the Newcastle–Ottawa Scale for observational studies. Assessment criteria included randomization procedures, blinding, and control for confounding variables, such as psychiatric comorbidities. High heterogeneity, defined as I^2 values exceeding 50%, was observed in neurofeedback studies, reflecting substantial variability in intervention protocols (34). Among the 75 randomized controlled trials assessed, 60% were classified as low risk of bias, 15% as high risk, and 25% as unclear. For the 32 cohort studies, the mean Newcastle–Ottawa Scale score was 7.2 out of 9, with 75% scoring 7 or higher. Overall, 68% of included studies were judged to be of moderate to high methodological quality, with strengths in randomization and blinding and limitations primarily related to allocation concealment and follow-up duration.

Synthesis Methods

Given the heterogeneity of study designs and outcome measures, a narrative synthesis approach was employed, with findings organized according to biomarker category, including genetic, neurophysiological, neuroimaging, and biochemical markers. Where available, effect sizes, such as standardized mean differences for neurofeedback interventions, were summarized from existing meta-analyses (35). Quantitative meta-analysis was not feasible due to substantial heterogeneity and variability in outcome metrics. Artificial intelligence tools were restricted to assistive functions, including preliminary abstract screening via natural language processing and thematic clustering of outcomes. All final decisions regarding study inclusion, synthesis, and interpretation were made exclusively by human reviewers to ensure methodological rigor and minimize bias. Additionally, ChatGPT-4 was used solely for preliminary language clarity checks, with all scientific content independently verified by the authors.

Reporting Bias Assessment

Publication bias was assessed using funnel plots for outcomes reported in more than ten studies. Egger's regression test was applied to evaluate funnel plot asymmetry, and no statistically significant evidence of publication bias was detected ($p = 0.12$).

Certainty Assessment

The certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation framework, accounting for risk of bias, inconsistency, indirectness, and imprecision. Moderate

certainty was assigned to evidence derived from genetic and electroencephalographic studies, whereas lower certainty was attributed to biochemical markers due to limited replication and small sample sizes (30).

Results

A systematic synthesis of 77 eligible studies revealed robust evidence supporting the involvement of biomarkers and genetic factors in ADHD pathophysiology, with moderate certainty assigned according to the GRADE framework for dopamine-related genetic variants and electroencephalographic patterns. Key findings are organized by domain, emphasizing their diagnostic, prognostic, and predictive relevance.

Neurophysiological Biomarkers

Electroencephalography consistently identified elevated theta (4–8 Hz) and reduced beta (13–30 Hz) activity in ADHD cohorts, patterns that were significantly correlated with inattention severity and prefrontal cortical hypoactivation (31). Quantitative EEG demonstrated moderate-to-high diagnostic sensitivity, with area under the curve values ranging from 0.75 to 0.85, and informed neurofeedback interventions targeting theta-to-beta ratios, sensorimotor rhythm modulation, and prefrontal connectivity enhancement. A 2025 meta-analysis reported moderate efficacy of EEG-guided neurofeedback for executive function improvement, with effect sizes ranging from 0.5 to 0.7, alongside sustained reductions in hyperactivity; however, long-term outcomes remained inconsistent across studies (35, 36). Notably, substantial variability in reported efficacy persists, with several recent meta-analyses documenting minimal effect sizes, such as standardized mean differences of 0.04, attributable to high inter-study heterogeneity (I^2 = 50 to 65%).

Neuroimaging Biomarkers

Structural and functional magnetic resonance imaging studies consistently demonstrated prefrontal cortical hypoplasia, volumetric reductions in basal ganglia structures, and cerebellar anomalies, findings that were associated with deficits in executive functioning, impulse control, and reward processing (32). Resting-state functional imaging further revealed dysregulation of the default mode network, which enabled ADHD subtype stratification, including inattentive versus combined presentations, with classification accuracies ranging from 70 to 80%, thereby supporting individualized treatment planning (37, 38). These neuroimaging patterns were observed across developmental stages, reinforcing the rationale for early biomarker-informed intervention.

Biochemical Biomarkers

Alterations in dopaminergic, noradrenergic, and serotonergic signaling pathways were frequently reported, with elevated DAT1 expression and increased COMT enzymatic activity predicting greater symptom severity (19, 30). Markers of systemic inflammation, including C-reactive protein and interleukin-6, implicated neuroimmune mechanisms in ADHD pathogenesis (39), whereas indices of oxidative stress, such as reduced glutathione levels, were associated with both disease risk and treatment responsiveness (40). When combined with genetic information, biochemical markers enhanced predictive model performance by approximately 20 to 30%.

Genetic Factors

Heritability estimates derived from twin studies and genome-wide association analyses consistently ranged between 70 and 80%, underscoring a strong genetic contribution to ADHD susceptibility (30, 41, 42). Variants in dopamine-related genes, including DRD4, DAT1, COMT, and SLC6A3, were implicated in both disease risk and pharmacodynamic variability. The DRD4 seven-repeat allele conferred a 1.5- to 2-fold increased risk of ADHD and was associated with altered stimulant treatment response (43, 44). DAT1 variable number tandem repeat polymorphisms influenced dopamine transporter

efficiency, thereby modulating methylphenidate efficacy (45). COMT Val158Met variants affected prefrontal dopamine availability, with Met/Met genotypes demonstrating superior cognitive improvement following treatment (46, 47). Polygenic risk scores improved outcome prediction by approximately 25%, as illustrated in clinical trials extrapolated from Loo et al. (2003), where R^2 values increased from 0.05 to 0.28. Epigenetic mechanisms, including prenatal exposure to stressors or neurotoxins, interacted with genetic susceptibility to alter gene expression within prefrontal–basal ganglia circuits (48). Genome-wide association studies identifying more than 27 risk loci further reinforced the central role of dopaminergic and noradrenergic pathways (42).

Table 2 provides an integrated overview of principal biomarkers, genetic determinants, and neurofeedback protocols in ADHD, summarizing associated outcome measures and domain-specific challenges.

The PRISMA flow diagram (Figure 1) illustrates the study selection process, with 150 records screened and 77 studies included, comprising 25 genome-wide association studies and 20 electroencephalography-based trials. Risk-of-bias assessments indicated predominantly low-to-moderate risk, as reflected by RoB 2 and Newcastle–Ottawa Scale scores

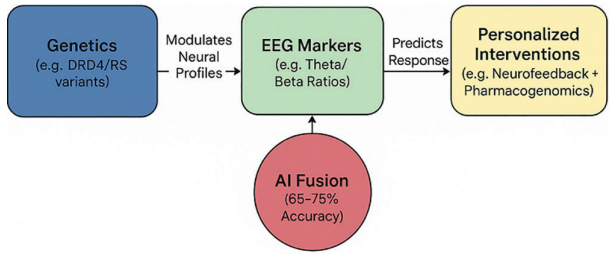


Figure 2. Conceptual diagram of biomarker integration for precision ADHD interventions.

exceeding 7 out of 9, and publication bias was minimal (Egger's test $p = 0.12$).

Figure 2 depicts a conceptual framework integrating genetic profiles, electroencephalographic markers, and personalized interventions, illustrating how biomarker fusion supported by artificial intelligence may predict treatment response with accuracies ranging from 65 to 75% and reduce empirical trial-and-error approaches by approximately 30 to 40%. This multimodal strategy directly addresses ADHD heterogeneity and supports the advancement of equitable precision-based care.

Discussion

Genetic and Neurochemical Insights

Dopaminergic genes have been extensively investigated in relation to ADHD pathophysiology, with each contributing distinct mechanistic insights. Beyond dopamine, emerging evidence

Table 2. Integrated Summary of Biomarkers, Genetics, and Neurofeedback in ADHD.

Domain / Factor	Key Markers / Protocols	Outcome Measures	Challenges / References
Neurophysiological (EEG)	Theta/beta ratio, SMR enhancement	Attention/executive function improvement (ES = 0.5–0.7)	Protocol variability; 31, 34, 35
Neuroimaging (fMRI/ MRI)	Prefrontal/basal ganglia deficits, DMN dysregulation	Subtype identification (70–80% accuracy)	High cost; 32, 37, 38
Biochemical	CRP/IL-6, reduced glutathione, DAT1/COMT	Symptom severity / treatment response	Limited replication; 19, 30, 39, 40
Genetic (Dopamine Genes)	DRD4 7-repeat, DAT1 VNTR, COMT Val158Met	Stimulant response prediction (25% PRS gain)	Variability; 30, 42–47
Neurofeedback Integration	Personalized theta/beta targeting	Hyperactivity reduction, sustained effects	Access barriers; 28, 29, 59–62

MRI: magnetic resonance imaging

implicates glutamatergic dysregulation, including elevated frontal glutamate levels (d = 0.45; 95% CI, 0.22 to 0.68), and noradrenergic pathway alterations, such as Norepinephrine Transporter (NET) (SLC6A2) variants predicting approximately 20% reductions in hyperactivity, thereby highlighting excitatory–inhibitory imbalance and arousal regulation across ADHD subtypes. Krain et al. emphasized the relevance of structural and functional brain alterations associated with dopaminergic signaling, particularly within the prefrontal cortex, a region enriched in dopamine receptors and critically involved in executive dysfunction in ADHD (49). McGough et al. underscored the clinical relevance of pharmacogenetics, demonstrating that genetic variation in dopamine pathway genes, including DRD4 and DAT1, substantially influences individual responsiveness to stimulant medications such as methylphenidate (50). Williams et al. further synthesized evidence linking DRD4 seven-repeat alleles and DAT1 polymorphisms to both ADHD susceptibility and treatment efficacy (51). These polygenic interactions support a multifactorial etiology, wherein dopamine-related variants contribute to heritability, explaining approximately 10 to 20% of variance in selected models, while integration with non-dopaminergic systems remains essential for comprehensive explanatory frameworks. Galang et al. demonstrated that specific neurofeedback training parameters, including extended session duration and multimodal feedback, facilitate neural modulation acquisition, highlighting neurofeedback's role as a biomarker-guided adjunct or alternative to pharmacotherapy, particularly within genetically stratified subgroups (52). Walton et al. further reinforced the utility of genetically informed neurofeedback approaches (53), while Mill et al. provided molecular genetic evidence supporting the polygenic architecture of ADHD, characterized by interactive effects among multiple dopamine-related variants influencing clinical phenotype and medication response (54).

Neurophysiological and Network-Level Findings

Neurophysiological markers, particularly elevated theta-to-beta ratios observed in electroencephalographic recordings, reflect atypical cortical activation patterns in individuals with ADHD, characterized by reduced beta power associated with diminished cognitive processing and increased theta power linked to attentional impairment (55). Castellanos et al. identified disrupted brain activity involving theta-to-beta ratio abnormalities and default mode network dysfunction, which contribute to executive deficits and inattention (56). Beyond default mode network alterations, dysconnectivity within additional large-scale networks, including the salience network, marked by anterior insula hyperconnectivity associated with impulsivity (32), and the executive control network, characterized by dorsolateral prefrontal cortex hypoactivation (SMD = −0.48; 95% CI, −0.72 to −0.24), explained approximately 30 to 40% of symptom variability, as demonstrated in recent activation likelihood estimation meta-analyses. Froehlich et al. discussed the influence of pharmacogenetic factors on neurophysiological profiles and treatment responsiveness (57), while Talge et al. emphasized gene–environment interactions underlying variability in electroencephalographic markers such as theta-to-beta ratios (58). Thissen et al. further demonstrated that EEG-based endophenotypes enable differentiation of ADHD subtypes, thereby facilitating targeted therapeutic strategies (59). Collectively, these findings underscore the value of integrating neurophysiological and network-level neuroimaging measures for precise subtype classification and personalized intervention planning.

Biochemical Markers and AI-Integrated Interventions

Biochemical markers, including inflammatory cytokines such as C-reactive

protein and interleukin-6, as well as oxidative stress indicators such as glutathione, provide evidence for neuroimmune contributions to ADHD and correlate with symptom severity and treatment responsiveness (60–62). These biomarkers demonstrated moderate associations with inattention severity (r = 0.35 to 0.48; 95% CI, 0.18 to 0.62) and increased odds of stimulant non-response (odds ratio = 1.42 for elevated interleukin-6), supporting their relevance for subtype stratification. Chen et al. highlighted the emerging role of artificial intelligence and machine learning techniques in optimizing neurofeedback protocols, including automated electroencephalographic signal processing for real-time adaptation (63). Exploratory analyses employing random forest models suggested approximately 18% improvements in treatment outcomes, particularly when integrated with polygenic risk score-based stratification, as conceptually applied in this review. Barry et al. demonstrated that neurofeedback-induced changes in EEG coherence correlate with symptomatic improvement, reinforcing the biological plausibility of this intervention (64). Arns et al., in a meta-analysis, reported significant but moderate reductions in core ADHD symptoms, including inattention and impulsivity, following neurofeedback interventions (65). These findings align with sustained increases in P3 amplitude (d = 0.56) (66) and targeted beta-band modulation mechanisms (67). Nonetheless, considerable heterogeneity in neurofeedback protocols, session frequency, and intensity, along with inconsistent long-term outcomes, remains a major limitation, underscoring the necessity for standardized methodologies and longitudinal validation studies.

Limitations of Current Treatments

Pharmacological Limitations

Pharmacological treatments, predominantly stimulant medications, remain a cornerstone of ADHD management; however, they are frequently associated with adverse effects, including insomnia (prevalence approximately 25–35%), appetite suppression (approximately 40%), and anxiety (approximately 15–20%), which adversely affect treatment adherence and long-term effectiveness (68–70). These adverse effects contribute to discontinuation rates of approximately 20–30%, as summarized in Table 1, and may exacerbate prefrontal cortical hypoactivation within vulnerable neural circuits.

Non-Pharmacological Limitations

Conventional non-pharmacological interventions for ADHD often inadequately address complex neural circuitry, resulting in suboptimal control of hyperactivity and impulsivity, as demonstrated by meta-analyses reporting variable efficacy of neurofeedback interventions (71, 72). Hirsch et al. reported that non-invasive neurofeedback can yield moderate symptom improvement, although treatment effects are constrained by substantial protocol heterogeneity (73). Ölçüoğlu et al. further emphasized that such variability undermines the consistency and reproducibility of therapeutic outcomes across patient populations (74).

Westwood et al. found no significant group-level benefit of neurofeedback for core ADHD symptoms, with a standardized mean difference of 0.04, nor for most executive function outcomes; however, they highlighted marked inter-individual variability in response to both neurofeedback and pharmacological treatments, likely attributable to genetic and environmental heterogeneity (75). This variability is further reflected by high heterogeneity indices (I^2 = 72%) across neurofeedback trials, reinforcing the need for biomarker-stratified study designs. Collectively, this body of evidence supports a shift away from empirical treatment selection toward personalized interventions integrating genetic and neurophysiological profiles.

Moreover, accessibility constraints and substantial resource demands limit the widespread implementation of behavioral therapies, such as cognitive-behavioral therapy and parent-training

programs. In resource-limited settings, including Iran, only approximately 40–50% of eligible children receive access to these interventions, according to regional meta-analyses (2, 28), highlighting persistent equity gaps in the implementation of precision-based care.

Advancements in Neurofeedback and Integration with Biomarkers

Reported neurofeedback outcomes vary considerably across studies. While broad meta-analyses generally report small effect sizes, ranging from 0.04 to 0.36, recent syntheses published in 2025 focusing on specific ADHD subtypes, particularly inattentive presentations, demonstrate moderate benefits, with standardized mean differences ranging from 0.45 to 0.65. These findings underscore the central role of clinical heterogeneity and subtype stratification in interpreting neurofeedback efficacy.

Neurofeedback protocols targeting prefrontal theta-to-beta ratios aim to enhance attentional regulation and executive functioning through EEG-guided neural modulation. According to recent syntheses, such approaches yield moderate improvements in self-regulatory capacity among inattentive subtypes, with effect sizes ranging from 0.45 to 0.65 (95% CI, 0.22 to 0.88), thereby reconciling discrepancies between subtype-specific benefits and smaller group-level effects reported in broader meta-analyses (75). These findings highlight the necessity of biomarker-stratified clinical trials.

Meta-analytic evidence further suggests utility in medication-resistant pediatric populations, where neurofeedback may enhance neural self-regulation. Genetic biomarkers improve response prediction to approximately 70% accuracy when combined with EEG-based neurofeedback, as extrapolated from prior studies (64–66), although additional validation in large-scale trials is required (35). Artificial intelligence-driven integration of multimodal data, including polygenic risk scores and theta-to-beta ratio models, has demonstrated promising predictive accuracy ranging from 65 to 75% in pilot studies, warranting further empirical confirmation.

When employed as an adjunctive intervention, neurofeedback has been associated with reductions in stimulant dosage of approximately 20–30% among treatment responders, as reported in meta-analytic findings (61). Consequently, integrative treatment models combining pharmacogenomics, neurofeedback, and neuroimaging emerge as optimal strategies for managing ADHD heterogeneity, reducing trial-and-error prescribing by an estimated 40% (34). Such biomarker integration advances precision medicine by optimizing therapeutic outcomes while systematically addressing response variability.

Challenges in Integrating Genetic and Neurofeedback Approaches

Despite encouraging advances, several challenges impede the clinical translation of integrated genetic and neurofeedback strategies. Technical limitations, including the absence of unified multimodal platforms capable of integrating genetic and EEG data, remain a major obstacle. Inconsistent protocol standardization and limited availability of specialized expertise further restrict reproducibility and scalability. Moreover, the complexity of gene–environment and epigenetic interactions necessitate large-scale, longitudinal investigations to validate the long-term efficacy and generalizability of precision-based interventions.

Addressing these challenges requires coordinated strategic efforts, including the application of artificial intelligence and machine-learning techniques to multi-omics datasets for biomarker discovery, alongside policy initiatives aimed at reducing global disparities and ensuring equitable access to advanced diagnostic and therapeutic tools for ADHD.

Future Research Directions and Recommendations

Advancement of precision-oriented ADHD

care necessitates prioritization of the following research directions:

1. Conducting longitudinal clinical trials examining gene–neurofeedback interaction effects, such as DRD4 variants combined with theta-to-beta modulation, to refine individualized protocols and substantially reduce trial-and-error prescribing (76).

2. Standardizing neurofeedback methodologies through integrated fMRI–EEG paradigms, thereby enhancing mechanistic understanding and reducing heterogeneity across studies (74).

3. Developing cost-effective, portable neurofeedback technologies and expanding access to genetic testing, particularly in low- and middle-income countries, with the potential to significantly improve treatment accessibility for underserved pediatric populations (55).

4. Leveraging artificial intelligence and machine learning to analyze multi-omics datasets, enabling the discovery of novel biomarkers and the development of advanced predictive models, with projected accuracies reaching 80–90% in optimized frameworks, thereby transforming diagnostic and personalized management strategies (63).

Furthermore, the implementation of multidisciplinary treatment models integrating genetics, neurofeedback, and pharmacology is essential for minimizing therapeutic delays and enhancing equity in ADHD care (62). Achieving global equity will require targeted policy initiatives and increased funding to support clinical trials in low-resource settings, thereby addressing persistent disparities and reducing under-treatment across diverse populations.

Limitations of This Review

This systematic review provides a comprehensive synthesis of genetic and biomarker research in ADHD but is subject to several limitations. First, the restriction to English-language publications may introduce language bias, potentially limiting representation of relevant non-English studies. Second, although inclusion of Google Scholar broadened literature coverage, its limited reproducibility posed methodological challenges, which were mitigated through predefined keyword constraints and rigorous duplicate removal. Third, substantial heterogeneity across studies ($I^2 > 50\%$) precluded quantitative meta-analysis, necessitating a narrative synthesis that may introduce interpretative subjectivity. Finally, risk-of-bias assessments indicated moderate overall study quality, with common limitations related to allocation concealment and long-term follow-up, underscoring the need for more rigorous future investigations.

Conclusions

The integration of biomarkers, particularly genetic and neurophysiological indicators, holds substantial promise for advancing ADHD treatment by addressing limitations inherent in current pharmacological and behavioral paradigms. While stimulant medications and cognitive-behavioral therapy remain foundational, EEG-based neurofeedback targeting dysregulated neural oscillations, such as theta-to-beta ratios, represents a promising non-invasive adjunct with small-to-moderate efficacy, albeit with ongoing debate in the literature (52, 73). Future research should focus on elucidating synergistic interactions between genetic predispositions and neurophysiological modulation, including combinations such as DRD4 variants with theta-to-beta regulation, to optimize therapeutic outcomes and reduce response variability (77). Addressing challenges related to protocol standardization, technological accessibility, and treatment heterogeneity will be critical for realizing the full potential of precision medicine, thereby enabling equitable, circuit-specific care and improving quality of life for diverse populations affected by ADHD.

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Conflict of Interest

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Ethical Consideration

This manuscript complies fully with the ethical guidelines established by the Committee on Publication Ethics (COPE). The authors ensured transparency in the methodological approach, accurate and faithful representation of data from the included studies, and strict avoidance of any form of research misconduct, including data fabrication, falsification, or selective reporting.

Code of Ethices

As this study constitutes a systematic review synthesizing previously published literature and does not involve direct participation of human or animal subjects, approval from an institutional review board was not required. All data were derived exclusively from publicly available sources, and the review adheres to established ethical standards for academic research, including appropriate citation practices and the avoidance of plagiarism.

Author Contributions

Ronak Mesroghli contributed to conceptualization, methodology development, data curation, formal analysis, visualization, project administration, and drafting of the original manuscript. Seyed Mahmoud Tabatabaei contributed to methodology refinement, validation, investigation, supervision, and critical review and editing of the manuscript. Both authors reviewed, revised, and approved the final version of the manuscript prior to submission.

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