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The Effectiveness of Genetic Factors on the Trainability of Individuals with Autism Spectrum Disorders: A Narrative Review

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Review Article

Abstract

Autism spectrum disorders connect to challenges like difficulties in movement. People with these disorders respond in unique ways to exercise and how they improve with practice. Scientists are learning that the genes people have at birth and other things affecting these genes might explain why individuals with autism spectrum disorders are so varied. The genes tied to these disorders are spread, with both common and rare differences showing up. Studies reveal that certain genes such as CNTF, AKT1, AMPD1, and APOE have a role in how much someone improves through exercise programs. These genes help us understand why exercise affects people. Exercise plays a role in helping people with Autism Spectrum Disorder through rehabilitation programs. Some researchers believe that polygenic risk scores and DNA methylation in genes like OXTR and BDNF have an influence on how effective these programs can be. Studying factors such as genes and DNA methylation may explain why some individuals with Autism Spectrum Disorder show better responses to exercise programs compared to others. This can provide insights into understanding trainability in autism. It also creates opportunities to explore tailored approaches in exercise and rehab programs.

Keywords: Autism spectrum disorders; Genetic variation; Trainability; Vo_2max; Epigenetics; Precision medicine

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Introduction

Neurodevelopmental disorders include many different conditions. These are marked by problems with thinking, communication, actions, or movement caused by unusual brain development (1). ASD is a wide group of neurodevelopmental conditions. ASD is characterized by persistent deficits in social communication and interaction, alongside restricted and repetitive patterns of behavior, motor impairments, and clinical symptoms that significantly impede functional performance across various life domains (2, 3).

Along with challenges in social skills and behavior, people with autism face motor development delays. They often take longer to sit and walk and struggle with motor planning and control (4, 5).

A review of studies shows that about 79% of people with ASD experience problems with motor skills. These difficulties lower their ability to handle everyday activities (4, 6). Experts need to focus on using functional strategies to enhance physical health and promote daily activities in ASD (7). Having motor function limitations is not always a main issue in ASD, but these individuals often face challenges when compared to neurotypical people. These individuals often exhibit impairments in postural control, dynamic balance, and gait patterns, alongside reduced joint

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flexibility and diminished movement velocity.

Many in this group commonly show less coordination, difficulties with both large and small movements, and repetitive or fixed motions (8-10). Joining physical activities can be tough for people with ASD because they face difficulties with motor skills, staying motivated, and controlling themselves.

Children and teenagers with autism take part in fewer physical activities because of challenges in social skills and behavior.

Such motor impairments often predispose individuals to a *sedentary lifestyle, leading to adverse health outcomes (11). Consequently, enhancing mobility and motor proficiency is essential for fostering institutional and environmental independence (12). In children with ASD, motor dysfunctions manifest in specific clinical forms that necessitate targeted interventions. A significant proportion of this population presents with hypotonia (reduced muscle tone) and motor apraxia (13). These deficits extend beyond basic locomotion, compromising overall physical fitness, postural stability, and equilibrium (14, 15). Furthermore, suboptimal lumbopelvic core stability—which serves as the primary anatomical stabilizer—is closely linked to impairments in both static and dynamic balance. Therefore, strengthening this region represents a critical therapeutic objective (16).

Integrating these children into structured physical activities is vital for concurrently enhancing social interaction and motor skill development (17, 18). Within this framework, alongside traditional therapeutic modalities, emerging technologies such as Active Video Games (AVGs) or Interactive Video Games have demonstrated potential in improving balance. These digital interventions offer a compelling and efficacious alternative to conventional group-based activities (19, 20).

Different methods help evaluate and develop motor skills in people with ASD (21). Genetics involves studying changes in DNA sequences that may raise the chance of neurodevelopmental disorders like ASD. Epigenetics, on the other hand, deals with changes in how genes work without altering the DNA sequence itself. These changes happen due to environmental or developmental influences (22, 23). These genetic and epigenetic factors together can shape a genetic risk profile. This profile reflects an individual's genetic predisposition to the disorder and underscores the potential severity of its clinical manifestations (24).

Leveraging advancements in identifying high-risk ASD susceptibility genes, researchers currently aim to elucidate the mechanistic pathways through which these variants drive the disorder, while investigating shared pathophysiological processes as potential molecular targets for therapeutic intervention (22). This deeper knowledge might help create new drugs that focus on the genetic and biological factors tied to ASD. This could result in better and more targeted treatments (25). Recent studies on genetics show that different genes linked to autism and other NDDs come together in certain important brain pathways. Researchers are now working to understand how these pathways overlap. Their goal is to use new technologies to make diagnosing and treating these conditions more accurate in the future (26).

People with neurodevelopmental disorders need repeated efforts to build and enhance their skills. Genetics plays a major role in this process. Sorting individuals by genetic differences helps create tailored strategies. New findings in genetic and epigenetic studies show how certain genetic changes and the interaction between genes and the environment affect how people with ASD can be trained. This research pushes us to rethink how genetics and epigenetics shape responses to exercise in ASD. Progress in medicine now focuses on improving synaptic activity and addressing neuroinflammation in ASD. Early tests of some new drugs show potential for reducing main symptoms and related challenges (27). The goal of this study was to examine and understand how genetic factors affect the trainability of people with ASD. The researchers aimed to explore how genes play a role in someone's ability and willingness to join exercise programs or therapeutic treatments. To investigate this, they reviewed and analyzed existing studies and research papers.

Genetics in People with Autism Spectrum Disorder

Twin studies and genome-wide research have played a big role in finding the genes linked to ASD. Molecular genetics has helped identify more than 100 genes tied to ASD. Rare and harmful mutations have been found in 10 to 25 percent of those with this condition (28).

In contrast, quantitative genetic studies demonstrate that while common genetic variants account for a substantial proportion of ASD heritability, the genetic architecture of the disorder remains remarkably heterogeneous (29). Recent large-scale genomic analyses, including Genome-Wide Association Studies (GWAS) and Whole-Exome Sequencing (WES), have further elucidated the complex genetic landscape of autism. Specifically, research by Grove et al. (30) and Fu et al. (31) has identified over 180 genetic loci associated with ASD risk. These loci encompass both common and rare

variants within critical synaptic genes, such as NRXN1, SYNGAP1, and DLG4.

Modern sequencing techniques, aided by technology, have shown that ASD is both polygenic and heterogeneous (33-37). However, in unusual situations such as Rett syndrome, Fragile X syndrome, Tuberous sclerosis, and Schuurs-Hoeijmakers syndrome, a single gene plays the main role in causing the disorder (4, 6-8). Over the past few decades, genetic linkage studies and GWAS have helped find many genetic loci. These findings include common single-nucleotide polymorphisms and rare copy number variations that have a strong influence (38-44).

Polygenic Risk Scores and Personalized Medicine

The Polygenic Risk Score (PRS) measures the total effect of many single-nucleotide polymorphisms (SNPs) linked to a condition like ASD. It shows the overall genetic load from common variants in the population (45). Along with rare genetic variants, PRS, which comes from adding up the effects of common variants found in GWAS, has a connection to ASD. In ASD, studies show PRS relates to phenotypic traits and biological structures. Its effect, together with rare variants, adds up to influence disease risk (46, 47). It makes sense to think that knowing more about genetic makeup can help create more tailored and successful treatments. Yet few studies have explored the use of genetic information, such as polygenic risk scores or specific genetic subgroups in people with autism, to guide treatment selection or development (24).

Notably, individuals with elevated polygenic risk scores (PRSs) for ASD and Attention-Deficit/Hyperactivity Disorder (ADHD) exhibit diminished responsiveness to group-based social skills training compared to standard care during follow-up assessments. This suggests that common genetic variants significantly modulate the efficacy of behavioral interventions (48). Such patterns align with previous findings regarding rare copy number variations (CNVs); specifically, carriers of pathogenic CNVs frequently demonstrate suboptimal outcomes following standard psychosocial interventions. These observations underscore the critical role of biological heterogeneity in determining inter-individual variability in treatment response among the ASD population (49, 50).

Epigenetics and Gene-Environment Interaction

Scientists studying epigenetics and genes that affect the nervous system have found DNA methylation changes unique to ASD. Brain samples from deceased ASD individuals showed more DNA methylation in the promoter regions of certain genes. This higher methylation is linked to lower expression of the oxytocin receptor (OXTR), Engrailed-2 (EN2), and Reelin (RELN) genes. The brain tissue of these individuals also exhibited high hydroxymethylation and increased MeCP2 protein binding in the promoter region of the Glutamate Decarboxylase 1 (GAD1) gene. These changes have an impact on gene silencing (51, 52).

Recent research reveals that epigenetic processes such as DNA methylation and changes to histones have a huge impact on how ASD develops. These processes can change due to factors in the environment and non-drug treatments, such as exercise (53, 54). Scientists have often found unusual methylation patterns in crucial genes that help brain growth and function in people with ASD. These genes include OXTR and BDNF. These odd patterns are linked to problems with social behaviors and the brain's ability to change and adapt (55-57).

Physical Activity in Individuals with Autism

ASD often features delayed motor function, and research reveals that teens with this condition perform worse on all physical fitness and motor skill tests (58, 59). Regular physical activity leads to health-related physical fitness, which includes factors like body composition, aerobic fitness (VO_2max), flexibility, and muscular fitness (60, 61). Experts use many tests to assess motor and physical skills in autistic children, including the Bruininks-Oseretsky Test of Motor Proficiency (BOT-2) (21). The good news is that studies on interventions show that well-planned and targeted exercise programs can greatly improve key aspects of motor function and core stability in children with autism (62).

The Impact of Physical Activity on Improving Autism Symptoms

Physical exercise interventions are a common way to improve ASD symptoms (63-65). Exercise boosts physical fitness and helps cut down on problematic behavior patterns (59). Motor problems show up and get worse as people age, so getting people moving should be a top priority (66). Also, people with ASD who do not move much face higher risks of heart disease, diabetes, and obesity; exercise can help prevent these issues (67). In particular, aerobic exercises have worked well to enhance balance, flexibility, and reduce repetitive movements and challenging behaviors (68-70).

The Link between Genes and How Well People with Autism Can Learn

Trainability shows how much an individual's fitness or skills can improve after a period of training (71). How well your heart and lungs work, as measured by VO_2max, predicts chronic disease and death risk

(72). People respond to exercise, and genes play a big part in this (73, 74). Studies looking at families, including twins and the HERITAGE Family Study, have found that genes account for up to 50% of VO_2max (75-77). The large HERITAGE study gives us the best proof of this. In this study, 473 white adults from 99 families followed a moderate-intensity aerobic exercise program for 20 weeks, which led to an average increase of 400 ml/min in VO_2max (75). New genetic tools like GWAS, RNA expression analysis, and whole-exome sequencing have improved our knowledge of the genetic basis of trainability and opened doors to develop personalized genomics (78). Yet, sports genomics research is still new, and using genetic tools to customize exercise programs for people with ASD needs more study.

Multi-omics approaches combine different layers of biological data. These include genomics, transcriptomics, epigenomics, and metabolomics. They help to identify complex molecular networks in neurodevelopmental disorders (79). Researchers now use these approaches more often to find molecular signatures. These signatures can predict how people with ASD will respond to treatments (80). Scientists aim to understand similarities within the wide range of autism differences. They want to uncover shared disease mechanisms and find classifying biomarkers. This could lead to targeted and personalized treatments. For instance, Matoba et al. mixed genomic and transcriptomic data. They found new genes and pathways linked to motor and cognitive outcomes in ASD (81).

Candidate Genes Associated with VO_2max and Autism

The candidate gene approach builds on the idea that specific genetic variations are linked to trainability traits. These variations serve as markers for unknown causal variants found in the population because of their genetic connection (82).

In this part, we look at key genetic variants that affect both trainability and how ASD develops (Figure 1). Because muscle function has an impact on VO_2max, experts think genes that code for muscle proteins play a part in how VO_2max trainability varies. The CARAGENE study examined how 12 genes and 21 genetic variants relate to muscle traits and trainability (83).

CNTF Gene: This gene encodes ciliary neurotrophic factor and has an impact on neurodegenerative disorders and neuron survival. Scientists have also linked its abnormal function to ASD (84, 85). Research by Thomas et al. (83) revealed that the variant (c.115-6G>A rs1800169) in this gene causes bigger shifts in relative VO_2max.

AMPD1 Gene: The *AMPD1* gene, located on chromosome 1p13, encodes the adenosine monophosphate deaminase (AMPD) protein. This protein catalyzes the conversion of adenosine monophosphate (AMP) to inosine monophosphate (IMP), a key step in the purine nucleotide cycle – a metabolic pathway intimately linked to energy utilization in muscle tissue. Research by Zhang et al. (86) suggests potential associations between variations in the *AMPD1* gene and autism spectrum disorder.

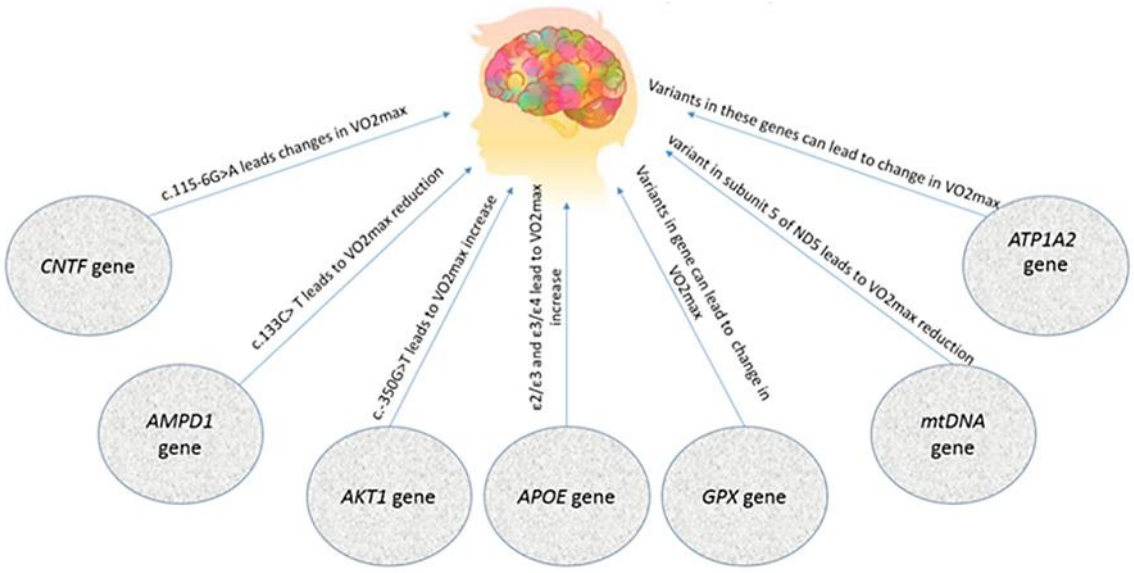

Figure 1. Genes and genetic variants that play a role in VO_2max trainability and might be linked to ASD

Building on this, Rico-Sanz et al. analyzed data from the HERITAGE study, examining individuals aged 17-65. Their findings revealed that participants with the TT genotype (AMPD1: c.133C>T, p. Gln45, rs17602729) – possessing two copies of the T allele – displayed a diminished physiological response to exercise after 20 weeks of moderate-intensity, steady-state training, compared to those with the CT or CC genotypes (87).

AKT1 Gene: Variations in the *AKT1* gene have been strongly implicated in the development of serious mental health disorders, including psychosis (such as schizophrenia) and bipolar disorder. Genetic studies and investigations of protein expression provide substantial evidence supporting the gene's critical role in the pathogenesis of these conditions (88, 89). Recent genetic findings further suggest that rare variants of *AKT1* may increase susceptibility to ASD, highlighting shared underlying biological processes between neurodevelopmental disorders and mental health conditions. Research by Onore et al. (90), examining the impact of disruptions in the Akt/mTOR signaling pathway in children with autism, supports this notion, indicating that genetic alterations within this pathway, including those affecting *AKT1*, may elevate ASD risk. Furthermore, studies exploring genes involved in related signaling pathways, such as PI3K/AKT/mTOR, have demonstrated their influence on ASD development, suggesting shared molecular features across neurodevelopmental and psychiatric disorders (91). The AKT protein family comprises three members: AKT1, AKT2, and AKT3, all of which participate in the phosphatidylinositol kinase (PI3K) and glycogen synthase kinase (GSK3) signaling pathways (92). Beyond its involvement in mental health, *AKT1* also influences skeletal muscle growth and differentiation. Jenkins et al. (93) demonstrated that individuals carrying the (TT/GT) genotype for the variant (AKT1: c.-350G>T, rs1130214) exhibited a greater increase in VO_2max after 24 weeks of moderate-intensity continuous training compared to those with the GG genotype.

ATP1A2 Gene: The ATP1A2 gene encodes the alpha-2 subunit of the Na+/K+ ATPase enzyme. This enzyme plays a crucial part in keeping electrolyte balance and muscle membrane excitability. Controlling sodium and potassium ions in active muscles has an impact on endurance performance and trainability. Research shows that genetic variations in this gene can affect how the body responds to physical activity and cardiorespiratory endurance. This happens by changing the metabolic features of skeletal muscle. These discoveries point to the essential role of ATP1A2 in determining endurance performance and how muscles adapt to exercise (94, 95).

APOE Gene: Aberrant DNA methylation patterns have been observed in central nervous system disorders (96). The *APOE* gene encodes a glycoprotein associated with lipoproteins in both the body and the brain (97). Research indicates that methylation of this gene can contribute to the development of Alzheimer's disease, suggesting potential shared pathological mechanisms with ASD (98). Different alleles of the *APOE* gene (ε2 and ε4) have been shown to influence the likelihood of developing ASD (98, 99). Furthermore, a study of Chinese individuals aged 18-40 demonstrated that those with *APOE* genotypes (ε2/ε3 and ε3/ε4) exhibited enhanced trainability compared to individuals with other *APOE* genotypes, a difference that became apparent following 6 months of progressively challenging moderate-intensity continuous training (100).

Oxidative Stress: Elevated oxidative stress is a contributing factor to neurodegenerative diseases (101). Individuals with these conditions frequently display altered levels of glutathione peroxidase (GPX) and selenoprotein P (Sepp) enzymes, with corresponding changes in the expression of their respective genes. Research has identified associations between specific *GPX* gene variants and the magnitude of VO_2max response to training (102).

Mitochondrial Dysfunction (MtD): MtD is implicated in approximately 5% of children with ASD (103). Deficiencies in mitochondrial function can manifest as neurological, behavioral, and metabolic alterations consistent with ASD symptomatology (104). These include activated microglia, reduced glutathione levels, repetitive behaviors, impaired social skills, hyperactivity, and oxidative stress (105, 106). Mitochondrial DNA (MtDNA) encodes several enzyme subunits crucial for oxidative phosphorylation and plays a significant role in determining endurance capacity and training responsiveness (107). In this context, Weller et al.'s research (108), investigating individuals with favorable responses to aerobic exercise, found that genetic variations within mtDNA are associated with the extent of VO_2max improvement. Notably, individuals who exhibit limited benefit from exercise tend to possess a greater number of polymorphisms at 13 specific loci within their mtDNA, including genes encoding proteins such as mt-ND1, mt-ND5, mt-CYTB, and hypervariable regions (HVRs).

Limitations

This study presents a narrative review, a format that differs from systematic reviews by lacking a

formalized quality assessment of included articles or meta-analysis. A primary limitation of this review is the scarcity of studies directly investigating the relationship between specific genetic variants and VO_2max response to exercise programs in individuals with ASD. Much of the supporting evidence presented concerning candidate genes—including *CNTF*, *AMPD1*, *AKT1*, and *APOE*—is derived from research conducted on general populations, rather than individuals with ASD. While the review subsequently explores potential links between these genes and the underlying biological processes of autism, few studies have directly quantified the impact of genetic variations on VO_2max improvements resulting from exercise interventions in individuals with autism. This limited data hinders the direct translation of sports genetics findings to the autism community. Furthermore, the review's focus primarily on VO_2max may not encompass other potentially relevant trainable areas, such as improvements in motor skills or reductions in repetitive behaviors, which may be influenced by distinct genetic factors. Given the rapidly evolving nature of this field, the review incorporates articles published up to July 2025 (48, 72-78, 83, 87, 93, 100, 108).

Recommendations

The findings from this review underscore a significant gap in our understanding of the interplay between genetics and exercise response in individuals with ASD. The observed heterogeneity in exercise responses—both motor and behavioral—among children with ASD highlights the need for a paradigm shift in research methodology. Rather than employing standardized exercise protocols, future studies should incorporate genetic markers associated with muscle function and neurodevelopment, such as variations in *AMPD1* and *CNTF* genes, to predict and explain individual outcomes. This approach could elucidate the reasons for variable improvements in areas such as balance and fitness, and clarify why some individuals experience substantial benefits from exercise while others do not.

Furthermore, given that the majority of current evidence regarding trainability originates from studies of non-autistic populations, rigorous preliminary assessments are essential to validate these findings within specific ASD subgroups. Detailed longitudinal tracking of participants' biological profiles during exercise programs represents a crucial step towards personalized rehabilitation and training plans. Finally, as the intersection of genetics and exercise science in autism remains relatively nascent, the development of theoretical frameworks elucidating how exercise modulates gene expression is paramount. Such frameworks will facilitate the design of targeted interventions, including precise prescriptions of exercise type, intensity, and duration, tailored to each individual's unique genetic profile.

Conclusion

The collective findings from the reviewed literature allow for the formulation of a preliminary theoretical framework suggesting that genetic factors may contribute to the heterogeneity in exercise responses, particularly in aerobic capacity, observed among individuals with ASD. However, it is crucial to acknowledge the limitations inherent in this synthesis, which draws upon disparate bodies of research – exercise genetics and autism biology – and therefore precludes definitive conclusions regarding the magnitude of genetic influence. The available evidence tentatively suggests that genetic variations and epigenetic modifications—changes in gene expression—may interact to modulate the physiological response to exercise in individuals with ASD. It is important to emphasize that this does not imply a causal relationship between genetic factors and these differences. To move beyond speculative hypotheses and translate these insights into clinical practice, a paradigm shift in research methodology is warranted. Rather than simply integrating findings from disparate fields, future studies should prioritize direct investigation of the interplay between genetic factors and training responsiveness within well-characterized ASD cohorts. This necessitates the development of research designs that incorporate genetic analyses alongside multidisciplinary perspectives to comprehensively elucidate underlying mechanisms, thereby enhancing the generalizability of findings.

In conclusion, while the prospect of personalized exercise interventions for individuals with ASD holds considerable promise, we remain in the early stages of conceptualizing this approach. Robust empirical evidence derived from rigorous studies is required before these concepts can be reliably applied in clinical rehabilitation settings, and careful consideration must be given to the ethical implications of utilizing individuals' genetic information.

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Conflict of Interest

The authors did not have a conflict of interest.

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