Current Perspectives on Autism Spectrum Disorder: Causes, Diagnosis, and Treatment

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Abstract

Autism spectrum disorder (also called ASD) is a pervasive disorder that strongly impacts the lives of affected individuals and their families. While the incidence of the disease has been increasing, little is understood about the exact mechanisms behind the disorder or how to treat it. Research must continue to determine the genetic and environmental factors that contribute to ASD. The methods of diagnosing ASD must also be scrutinized. Developments in these areas could greatly impact the lives of people who have ASD. Knowledge of the underlying mechanisms could provide the key to biological treatment, while more specific diagnoses could allow for greater distinction between individuals on the spectrum based on their personal abilities and needs. Additionally, research into pharmacologic, therapeutic, and non-invasive treatments could improve the quality of life for individuals who have ASD. The present paper seeks to synthesize current research on the causes, diagnosis, and treatment of autism spectrum disorder, then propose directions for future research. Through a detailed examination of the current literature, new directions will be determined.

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social-emotional reciprocity, nonverbal communicative behaviors, or understanding and maintaining relationships (Centers for Disease Control and Prevention, 2016). In addition to the social impairments, ASD diagnostic criteria include restricted or repetitive behaviors and interests (Centers for Disease Control and Prevention, 2016). These symptoms can manifest as abnormal social interactions, ritualized behaviors or routines, and stereotyped movements or speech (Centers for Disease Control and Prevention, 2016). These and other behaviors can negatively impact social, occupational, and other areas of functioning (Centers for Disease Control and Prevention, 2016).

Genetic Causes of ASD

Current research suggests that ASD is caused by both genetic and environmental factors, though the exact etiology is unknown. Genetic factors have been shown to influence ASD susceptibility; siblings of individuals with a confirmed ASD diagnosis have a greatly increased risk of diagnosis compared to the rest of the population (Hodges et al., 2020). Under the DSM-IV diagnostic criteria, 88% of monozygotic twins and 31% of dizygotic twins showed ASD concordance (where both individuals were affected, although presentations varied) (Rosenberg et al., 2009). Additionally, there are strong genetic correlations between ASD and other complex diseases, such as schizophrenia, major depression, anxiety, and ADHD (attention-deficit/hyperactivity disorder) (Grove et al., 2019). Psychiatric comorbidities are also noteworthy in ASD. A recent meta-analysis estimated up to 27% prevalence of psychiatric

comorbities including ADHD, intellectual disability, anxiety disorders, sleep disorders, bipolar disorders, and depression (Mutluer et al., 2022). One study found as high as a 59% comorbidity rate for ADHD in individuals diagnosed with ASD (Stevens et al., 2016). Additionally, the analysis revealed a significant delay in the age of first seeking medical assistance and the age of ASD diagnosis for individuals who were also diagnosed with ADHD (Stevens et al., 2016).

Recently, genome-wide association studies have allowed researchers to identify numerous genome-wide significant markers in ASD and select candidate genes that may be implicated in the disorder (see Figure 1) (Grove et al., 2019). These candidate genes play roles in brain development, neurotransmitter function, neuronal excitability, or building proteins relevant to the neuronal synapse (Hodges et al., 2020). Epigenetic mechanisms may also be involved, including DNA methylation or histone acetylation and modification (Hodges et al., 2020). Recent research has identified differential DNA methylation among twins with discordant ASD diagnoses and autistic traits (Myers et al., 2021). Continued research may provide insight into the specific genetic mechanisms responsible for ASD. Identifying genes involved in the manifestation of ASD is only the first step to understanding the biological causes or treatments of the disorder.

Environmental Causes of ASD

Despite the clear impact of genetics on ASD, the effect is modulated, to an extent, by prenatal, perinatal, and postnatal environmental factors (Hodges et al., 2020). Genetic susceptibility produces a wide range of phenotypic expressions. Researchers must continue to study the precise combination of environmental influences on ASD.

Figure 1: Candidate genes for ASD (Grove et al., 2019).

Box 1 | Selected loci and candidates (ordered by chromosome)

Gene	Locus[a] and supporting evidence	Gene function
NEGR1	Chr 1:72729142 Shared ASD-MDD locus This locus is also significant in depression[25,57], educational attainment[21], intelligence[41], obesity, and BMI[29,58–61], and in an ASD-schizophrenia meta-analysis[5]. *NEGR1* is the only protein-coding gene in the locus. *NEGR1* is supported by brain Hi-C and eQTL analyses[25].	Neuronal growth regulator 1 (NEGR1) is an adhesion molecule modulating synapse formation in hippocampal neurons[62,63] and neurite outgrowth[64,65]. It is a member of the IgLON protein family, which is implicated in synaptic plasticity and axon extension[66–68] NEGR1 is predominantly expressed (and developmentally upregulated) in the hippocampus and cortex[69], as well as the hypothalamus[70]
PTBP2	Chr 1:96561801 ASD locus This locus is also significant in BMI[29,58,60] weight[58], and educational attainment[21]. In schizophrenia, the locus shows a *P* value of 6.5×10^{-6} (ref. [15]). *PTBP2* is the nearest protein-coding gene, ~625 kb from the index SNP. De novo and rare variants in *PTBP2* have been reported in ASD cases[1,3,71]. *PTBP2* is supported by Hi-C results in this study (Fig. 5d).	PTBP2, also known as nPTB (neuronal PTB) or brPTB (brain PTB), is a splicing regulator. PTBP1 and its paralog PTBP2 bind intronic polypyrimidine tracts in precursor mRNAs and target large sets of exons, thereby coordinating alternative-splicing programs during development[72]. Several switches in the expression of PTBP1 and PTBP2 regulate alternative splicing during neurogenesis and neuronal differentiation[73–76].
CADPS	Chr 3:62481063 Shared ASD-Edu locus This locus is also significant in a study of cognitive-decline rate[77]. *CADPS* is supported by Hi-C results in this study (Fig. 5a).	*CADPS* encodes a calcium-binding protein involved in exocytosis of neurotransmitters and neuropeptides. In line with *CAPDS* mRNA being mainly expressed in the brain and pituitary (GTEx portal; see URLs), immunoreactive CAPS-1 is localized in neural and various endocrine tissues[78]. In hippocampal synapses, CADPS regulates the pool of readily releasable vesicles at presynaptic terminals[79,80]
KCNN2	Chr 5:113801423 ASD locus (gene-wise analysis) This locus is also significant in educational attainment[21,81]. KCNN2 synaptic levels are regulated by the E3 ubiquitin ligase UBE3A[82], whose overexpression has been linked to ASD risk[82,83].	KCNN2 is a voltage-independent Ca^{2+}-activated K^+ channel that responds to changes in intracellular calcium concentration and couples calcium metabolism to potassium flux and membrane excitability. In central-nervous-system neurons, activation of KCNN2 modulates neuronal excitability by causing membrane hyperpolarization[84]. Hippocampal KCNN2 has roles in the formation of new memory[85], encoding and consolidation of contextual fear[86], and in drug-induced plasticity[87].
KMT2E	Chr 7:104744219 ASD locus This locus is also significant in schizophrenia[15,88] and in ASD-schizophrenia meta-analysis[5]. *KMT2E* de novo mutations are associated with ASD at FDR <0.1 (ref. [35]). A *KMT2E* credible SNP is a loss-of-function variant (Supplementary Table 16).	*KMT2E* encodes histone-lysine N-methyltransferase 2E and forms a family together with SETD5 (refs. [89,90]). Evidence suggests that recognition of the histone H3K4me3 mark by the KMT2E PHD finger can facilitate recruitment of KMT2E to transcription-active chromatin regions[91,92]. KMT2E has been implicated in chromatin regulation, control of cell-cycle progression, and maintaining genomic stability[93].
MACROD2	Chr 20:14836243 ASD locus This locus is significant in previous ASD GWAS[94] but not supported in larger study[95]. *MACROD2* is the only protein-coding gene in the locus.	MACROD2 is a nuclear enzyme that binds mono-ADP-ribosylated (MARylated) proteins and functions as an eraser of mono-ADP-ribosylation[96]. Intracellular MARylated histones and GSK3β are substrates of MACROD2, and the removal of MAR from GSK3β is responsible for reactivation of its kinase activity[96]. This gene is expressed in the lung and multiple regions of the brain but has low or no expression across most other tissues (GTEx portal; see URLs).

[a]Position of index SNP is listed. Chr, chromosome.

External risk factors such as advanced paternal or maternal age or prenatal exposure to thalidomide and valproic acid have been shown to increase the risk of ASD (Hodges et al., 2020). Other factors including maternal history of autoimmune disease, infection during pregnancy, or prenatal factors such as maternal anemia, toxic chemical exposure, and maternal diabetes are also being studied (Carlsson et al., 2020 & Hodges et al., 2020). These various

environmental factors relate to ASD development in poorly understood ways and their interaction presents a challenge in identifying the causes of the disorder. Prenatal diet may be a potential therapeutic target for mitigating environmental risk factors such as air pollutants, endocrine-disrupting chemicals, pesticides, and heavy metals (Bragg et al., 2022). The complicated interplay between genetic and environmental influences in the development of ASD is poorly understood. As an individual with ASD ages, their surrounding environment continues to impact them and shape their personality and behaviors. Inflammation, autoimmunity, and the gut-brain axis have also been implicated in the pathogenesis of ASD (Doenyas, 2018). Environmental pre- and post-natal factors present a future direction in the study of ASD prevention and management.

Diagnosis

Autism is considered on a spectrum due to heterogeneity in the presentation and severity of symptoms and the varying levels of functioning seen in individuals who have ASD (American Psychological Association, 2013). In accordance with the DSM-5, ASD is diagnosed based on behavioral and social symptoms (see Figure 2). Diagnostic criteria include persistent deficits in three areas of social communication and interaction, as well as at least two types of restricted, repetitive behaviors. Deficits in social behaviors include difficulty with social-emotional reciprocity, non-verbal communication, or understanding relationships. Examples of repetitive behaviors are stereotyped motor movements or speech, ritualized patterns of behavior, highly restricted interests, or hyper- or hyporeactivity to sensory input. These core symptoms are further specified by severity based on the level of support that the individual requires. The DSM-5 also

details the notation of accompanying intellectual impairment, language impairment, catatonia, and associated medical conditions or other disorders.

Figure 2: DSM-5 Diagnostic Criteria for ASD (CDC, 2016).

The general pediatric population is screened for ASD with developmental surveillance and autism-specific screenings up to 30 months of age (Hodges et al., 2020). Screening tools for ASD in young children include the Modified Checklist for Autism in Toddlers, Revised, with

Follow-up (M-CHAT-R/F), and the Survey of Wellbeing in Young Children (SWYC) (Hodges et al., 2020). Early signs suggestive of ASD include poor eye contact, poor response to name, lack of sharing, no gesturing by 12 months, and lack of language or social skills. As a child ages, other screening tools such as the Social Communication Questionnaire (SCQ), Social Responsiveness Scale (SRS), and Autism Spectrum Screening Questionnaire (ASSQ) may also be used (Hodges et al., 2020). Primary care clinicians refer children who may have ASD to early intervention programs and a specialist who can provide a definitive diagnosis and comprehensive assessment. The specialist assessment should include a physical exam, a full neurological examination, a Wood's lamp examination of the skin, a parent interview, and an observation of the child's cognitive, language, and adaptive functioning (Hodges et al., 2020). Primary care clinicians will also evaluate for potential co-occurring medical, developmental, and psychiatric conditions.

ASD is typically diagnosed around 3-5 years of age. Early intervention in ASD is associated with positive outcomes in adaptive functioning and intelligence quotient and reduced behavioral and functional impairments (Leader et al., 2021). Interestingly, ASD is diagnosed much more often in males than females (at a ratio of 3:1) (Hodges et al., 2020). The mechanism behind this disparity is not fully understood. It is also noteworthy that the female autism phenotype differs from that of males. These differences and unconscious bias can hinder the diagnosis and treatment of ASD in females compared to males. The high level of heterogeneity between individuals who have ASD, in terms of presentation and level of functioning, makes diagnosis difficult. Furthermore, treatment is extremely challenging due to the heterogeneity in symptoms and severity between individuals with a confirmed ASD diagnosis.

Treatment of ASD

Current treatments for ASD vary from therapy to pharmacology. Evidence-based therapeutic options which can help improve adaptive behavior and reduce ASD severity include applied behavioral analysis (ABA), occupational therapy (such as Ayres Sensory Integration (ASI) or Sensory Integration Therapy (SIT)), and speech pathology (if it would be beneficial). Theory of Mind Training has also shown promising results in improving empathetic understanding and responsiveness (Holopainen et al., 2018). Other non-invasive treatment options are probiotics or prebiotics as they have been shown to have significant effects on all domains of the Autism Treatment Evaluation Checklist (ATEC) (Azari et al., 2022). Lifestyle choices that may improve ASD traits and quality of life include antioxidant supplementation or regular physical activity or exercise (Toscano et al., 2017 & Manivasagam et al., 2020).

Certain drugs are being researched in the treatment of ASD, but most target specific symptoms and there is no medication approved for the treatment of core symptoms (social communication difficulties and repetitive behaviors). Medications that could improve at least one core symptom of ASD include aripiprazole, atomoxetine, bumetanide, or risperidone for children, and fluoxetine, fluvoxamine, oxytocin, or risperidone for adults (Siafis et al., 2022). Pharmacologic treatments for behavioral symptoms of ASD that are being studied include antipsychotics for irritability, psychostimulants for hyperactivity or inattention, D-cycloserine, and memantine for social impairment (Doyle & McDougle, 2012). Much more research is necessary before these treatments become widespread because they treat specific symptoms rather than the entire individual or the root of the symptoms, and the effects may vary for each person. Furthermore, many of the medications have side effects that could negatively impact the quality of life for the individual while trying to treat symptoms.

Results

Genetic Causes

A comprehensive understanding of the genetic mechanisms behind ASD would allow for the development of targeted pharmacologic treatments. Furthermore, identification of the genes involved could promote discrimination between cases of ASD with unique genetic etiology. Pharmacological treatment based on the discrete pathophysiology of the individual could yield more effective results while minimizing risk and unpleasant side effects. Treatment options could be more clearly identified after unraveling the complicated genetic and epigenetic mechanisms which play a role in ASD. Additionally, knowledge of the genetic mechanisms involved could provide key insight into how environmental factors interact with genotype in the development of the disorder. Biological differences have been noted between individuals who have ASD and people who do not. These physiological differences include brain structure and function and gut-brain axis disparities. They may also influence the co-occurrence of other diseases in addition to ASD (psychiatric and other neurodevelopmental disorders, such as ADHD and Rett syndrome).

Genetic analysis and counseling may also benefit individuals with ASD. Currently, genetic testing can provide patients counseling regarding recurrence risk for those who already have a child with ASD, early identification of children with genetic susceptibility to ASD, and a clear genetic diagnosis (Miller, 2010). Early identification of genetic susceptibility facilitates early behavioral intervention which can improve developmental outcomes. Also, a genetic diagnosis can qualify a child for treatment at an earlier age before more severe symptoms develop or a clinical diagnosis can be made. The heterogeneity in ASD genotype and phenotype

makes genetic testing extremely difficult. If the various genetic mechanisms behind ASD could be identified and distinguished, genetic testing could provide a more definitive ASD diagnosis much earlier and increase access to early intervention.

Brain Structure

The structural and functional brain abnormality in ASD is the underconnectivity of cortical systems and overgrowth of neurons (especially in the prefrontal cortex). This is supported by task-related functional connectivity (fc) fMRI studies which found reduced synchronization between co-activating cortical areas in individuals with ASD (Minshew & Keller, 2010). Additional fMRI studies showed enhanced activation of occipitoparietal areas proposed to result from increased local connectivity in the posterior of the brain (Minshew & Keller, 2010). It is hypothesized that the engagement of posterior regions with weak connections to the frontal language areas leads to reliance on visual mediation for cognitive tasks (Minshew & Keller, 2010). This explains why visual aids are one recommended strategy to improve communication with people who have ASD. Various fMRI studies have also identified disturbances in integrative information processing, although remediation was effective and resulted in measurable improvements (Minshew & Keller, 2010). Research has demonstrated significantly decreased functional connectivity across the motor execution network and broad neuronal dysfunction across disparate cortical areas (Minshew & Keller, 2010).

Structural imaging data have shown accelerated brain growth beginning at the same time as the onset of ASD symptoms, and increased total cerebral gray and white matter (Minshew & Keller, 2010). Another study found abnormal laminar architecture and cortical disorganization of neurons in prefrontal and temporal cortical tissue from children with ASD (Stoner et al., 2014).

They concluded probable dysregulation of brain layer formation and layer-specific neuronal differentiation during prenatal development (Stoner et al., 2014). The social impairment in ASD is related to deficits in theory of mind (the ability to understand what other people know and feel), dysfunctional reward processing, and underactivation of the fusiform gyrus (essential for face processing and recognition) (Minshew & Keller, 2010). These structural and functional features of the brain in ASD require additional study and could contribute to a biological explanation of the symptoms of ASD.

Gut-Brain Axis

Biological comorbidities noted in individuals who have ASD include inflammation or immune system dysregulation and gut microbiota abnormalities. Children with ASD experience notably more gastrointestinal (GI) symptoms than children without, and these GI symptoms strongly correlate with ASD severity (Doenyas, 2018). Short-chain fatty acids produced by gut bacteria have also been indicated to contribute to ASD pathology (these include butyric, propionic, acetic, and valeric acid) (Liu et al., 2022). Although the exact gut microbiota profile of ASD is unclear, numerous studies have attempted to classify the altered gut microbiota with varying results (see Figure 3 for a summary of ASD gut microbiota composition findings). Gut microbiota also regulate the gut barrier and are important for many biological and metabolic functions. Gut dysbiosis disturbs gut-brain communication. Furthermore, decades of research support an association between ASD and immune dysregulation or inflammation (Doenyas, 2018). The immune system is considered one route in gut-brain communication; both microbiota and inflammation can influence synaptic transmission and connectivity. The gut-brain axis (bi-directional communication between the brain and the gut) and, in a connected manner,

inflammation may be involved in core and associated ASD symptoms. Furthermore, dysfunction of the gut-brain axis has been implicated in various other psychiatric and non-psychiatric disorders (Vellingiri et al., 2022). Gut-brain axis abnormalities are likely related to the prevalence of psychiatric comorbidities in ASD.

Figure 3: ASD microbiota composition (Liu et al., 2022)

Study subjects	Findings	References
13 autistic children and 8 control children	*Clostridium*↑ and *Ruminococcus* spp.↑	Finegold et al. (2002)
15 autistic children and 8 control children	*C. bolteae*↑, *Clostridium* clusters I↑, and *Clostridium* clusters XI↑	Song et al. (2004)
58 autistic children, 12 healthy siblings, and 10 control children	*Clostridium* clusters I↑ and *Clostridium* clusters II↑	Parracho et al. (2005)
33 autistic subjects,7 sibling controls, and 8 non-sibling control subjects	*Bacteroidetes*↑, *Proteobacteria*↑, *Alkaliflexus*↑, *Desulfovibrio*↑, *Acetanaerobacterium*↑, *Bacteroides*↑, *Parabacteroides*↑, *Desulfovibrio* spp. ↑, *Bacteroides vulgatus*↑, *Actinobacteira*↓, *Turicibacter Clostridium*↓, *Firmicutes*↓, *Weissella*↓, *Helcococcus*↓, *Alkaliphilus*↓ *Anaerofilum*↓, *Pseudoramibacter*↓, *Ruminococcus*↓, *Streptococcus*↓, *Anaerovorax*↓, *Dialister*↓, *Lactococcus*↓, *Leuconostoc*↓, and *Ethanoligenens*↓	Finegold et al. (2010)
15AUT-GI and 7 control-GI children	*Betaproteobacteria*↑, *Bacteroidetes*↓, and the ratio of *Firmicutes/Bacteroidetes*↑	Williams et al. (2011)
10 autistic children, 9 siblings, and 10 healthy children	*Lactobacillus* spp.↑, *Desulfovibrio* spp.↑, and *Bacteroidetes/Firmicutes*↓	Tomova et al. (2015)
35 children with ASD and 6 TD children	*Sutterella*↑, *Odoribacter*↑, *Butyricimonas*↑, *Veillonella*↓, *Streptococcus*↓, and *Bacteroidetes/Firmicutes*↑	Zhang et al. (2018)
48 children with ASD and 48 healthy children	*Firmicutes*↓, *Proteobacteria*↓, *Verrucomicrobia*↓, *Bacteroidetes/Firmicutes*↑, *Dialister*↓, *Prevotella*↑, *Bacteroides*↑, *Megamonas*↑, *Escherichia/Shigella*↓, *Lachnospiracea_incertae_sedis*↑, *Clostridium XlVa*↓, *Eisenbergiella*↓, *Clostridium IV*↓, *Flavonifractor*↓, *Haemophilus*↓, and *Akkermansia*↓	Zou et al. (2020)
77 children with ASD and 50 age-matched healthy children	*Unidentified Lachnospiraceae*↑, *Clostridiales*↑, *Dorea*↑, *Erysipelotrichaceae*↑, *Collinsella*↑, *Lachnoclostridium*↑, *Bacteroides*↓, *Faecalibacterium*↓, *Parasutterella*↓, and *Paraprevotella*↓	Ding et al. (2020)
9 autistic children, and 6 healthy children	*Bacteroidales* ↓, *Selenomonadales*↓, *Prevotellaceae*↓, and *Ruminococcaceae*↑	Sun et al. (2019)
143 ASD children, 143 age- and sex-matched TD individuals	*Firmicutes*↑, *Firmicutes/Bacteroidetes*↑, *Megamonas*↓, *Proteobacteria*↑, *Actinobacteria*↑, *Bacteroidetes*↓, *Dialister*↑, *Escherichia-Shigella*↑, *Bifidobacterium*↑, *Prevotella* 9↓, and *Ruminococcus* 2↓	Dan et al. (2020)
72 ASD and 74 TD children	*Clostridium*↑, *Dialister*↑, *Coprobacillus*↑, and *Faecalibacterium*↓	Wan et al. (2021)
11 ASD and 14 healthy control children	*Actinobacteria*↓, *Bacteroidetes*↑, *Proteobacteria*↑, *Bacteroidetes/Firmicutes*↑, *Actinomycetaceae*↓, *Coriobacteriaceae*↓, *Oscillospira*↑, *Gemellaceae* ↓, *Streptococcaceae*↓, *Faecalibacterium prausnitzii*↑, and *Bifidobacteriaceae*↓	Coretti et al. (2018)

Environmental Considerations

A person's environment influences their development and behaviors. ASD is a life-long condition and affected individuals often require continued support. Research indicates that while functional connectivity and distribution of brain activation differ between participants with ASD and participants who are neurotypical, differences between children and adults who have ASD

suggest positive changes in language processing neural functioning associated with maturation and/or educational experience (Williams et al., 2013). Still, although the majority of high school students with ASD are on the diploma track in the United States, post-secondary outcomes are poor (Lee et al., 2022). This includes vocational outcomes; with only a third of young adults employed 8 years following high school graduation (Lee et al., 2022). Research must be conducted into accommodation for and acceptance of individuals with ASD in the workforce. Comparable advancements have occurred in accessibility of higher education, though organizational and social change must continue to allow these programs to flourish.

Attention must also be devoted to removing barriers to healthcare as an individual with ASD ages. Common barriers to accessibility include a shortage of services, the cost of services or limited insurance, physician knowledge of ASD, and social stigma (Malik-Soni et al., 2021). For example, the annual healthcare costs for individuals who have ASD increase with age and are estimated to be $13,580 for individuals aged 18 and older (Malik-Soni et al., 2021). Adults who have ASD often encounter other health issues affecting their physical and mental health, and have an increased risk of premature mortality compared to the general population (mean age of mortality: 54 vs 70 years, 40 years for those who are low functioning) (Malik-Soni et al., 2021). Research should aim to develop interventions to support individuals who have ASD through the transition to adulthood and improve health outcomes in adults.

Diagnosis

The diagnostic criteria for ASD need modification to adapt to the realistic needs of the population. The criteria presented in the DSM-5 (and primarily used to diagnose ASD) are behavioral observations and subject to low interrater reliability (degree of agreement between

different examiners). Additionally, differences in sex, race, ethnicity, and primary language can impede diagnosis. The female ASD behavioral phenotype has significant differences from that of males. Females are also more likely to engage in camouflaging (masking ASD traits). Studies have suggested that this may lead to girls being misdiagnosed, diagnosed later, or overlooked entirely (Hodges et al., 2020). Others also question if the diagnostic criteria may be biased to represent the male phenotype. Similarly, ASD is present in all populations, but more consistently identified in Caucasian children (Hodges et al., 2020). The presence of psychiatric comorbidities also makes ASD more difficult to diagnose, often by overlapping or masking symptoms. Research has shown that the age of ASD diagnosis is significantly later in children who have a comorbidity (as long as three to four years) (Leader et al., 2021). Awareness and provider knowledge/assessment of ASD comorbidities must increase in order to provide accurate diagnoses and provide the best quality treatment to each individual.

Multiple scales are often used to assess ASD severity and behaviors. One scale defined by empirical research is the Childhood Autism Rating Scale (CARS2). The Autism Diagnostic Observation Schedule (ADOS) is a standardized diagnostic test for ages one year through adulthood. These and other ASD assessments which are empirically proven should be made accessible to healthcare professionals and specified ASD training should be provided. Using a combination of proven rating scales can give clinicians a better understanding of their patient's ASD status, severity, symptoms, and needs.

The development of a biological way to diagnose ASD could increase the specificity of diagnoses on the autism spectrum and reduce heterogeneity between subgroups, clarifying treatment options on an individual basis. Potential biological-based diagnostic criteria could include autonomic nervous system, gut-brain axis, blood, or protein biomarkers (Kong et al.,

2020 & Yao et al., 2021). The autonomic nervous system (ANS) is a part of the gut-brain axis. The gut microbiome and autonomic indices could serve as non-invasive biomarkers for gut-brain axis status in ASD. Recent studies have uncovered ANS abnormalities in individuals with ASD (Kong et al., 2020). Instability of the ANS could be related to the high prevalence of psychiatric comorbidities in individuals who have ASD (Kong et al., 2020). ANS dysfunction may also influence the high prevalence of cardiovascular mortality and morbidity in individuals with ASD (Kong et al., 2020). Potential blood protein biomarkers that indicated significant power in discriminating ASD cases are SLC25A12, LIMK1, and RARS (see Figure 4 for the six protein biomarkers tested and their function) (Kong et al., 2020). A recent study also found an association between later ASD diagnosis and neonatal cerebrospinal fluid concentration of arginine vasopressin (Oztan et al., 2020). These and other quantifiable, biological features should be the future of ASD diagnosis as soon as they can be verified scientifically.

Figure 4: Six predicted blood-secretory protein biomarkers for ASD (1, 5, and 6 significant) (Kong et al., 2020).

No.	Gene	UniProt ID	Protein[a]	Function[b]
1	*RARS*	P54136	Arginine–tRNA ligase, cytoplasmic	Protein synthesis, inflammatory
2	*ACTL6B*	O94805	Actin-like protein 6B	Transcriptional activation and chromatin remodeling
3	*ARHGEF4*	Q9NR80	Rho guanine nucleotide exchange factor 4	High levels in the brain and is involved in cell migration and cell–cell adhesion
4	*PRKAA1*	Q13131	5′-AMP-activated protein kinase catalytic subunit alpha-1	Cellular energy metabolism, cell growth and proliferation, phosphorylation
5	*SLC25A12*	O75746	Calcium-binding mitochondrial carrier protein Aralar1	Calcium ion binding, amino acid metabolism
6	*LIMK1*	P53667	LIM domain kinase 1	Stimulates axonal outgrowth and may be involved in brain development

[a] Except RARS did not match the two databases (i.e., AutismKB and plasma protein database), all the other proteins were matched. However, RARS has important functions and may be implied in the pathogenesis of ASD.
[b] Functional information obtained from UniProt database (https://www.uniprot.org/).

Treatment

Future directions of ASD treatment should prioritize individualization to meet the specific needs of the patient. Additionally, treatment should address the whole person and all aspects of their diagnosis. Measureable biological features and concurrent disorders should also be considered in the treatment of ASD. Knowledge of comorbidities informs prescribing decisions and minimizes the risk of adverse side effects. ASD treatment should treat the whole individual by coordinating available treatments, such as concurrence of behavioral therapy and speech pathology. The benefists and risks of various forms of treatment should be considered for each individual and planned with their best intentions in mind.

Interventions targeting common mechanisms of action in ASD could also provide more widespread alleviation of symptoms while minimizing the risk to inidividuals seeking treatment. One example of a treatment that targets a common mechanism of action in heterogeneous cases of ASD is probiotics (live microbes that have health benefits when consumed) (Doenyas, 2018). Gut microbiome corrections, such as probiotics, have potential to improve symptoms of psychiatric disorders, including ASD (Soltysova et al., 2022). Other microbial-based therapeutic interventions include prebiotics, antibiotics, fecal microbiota transplantation therapy, and dietary interventions (Liu et al., 2022). While results have been prominsing, a lot of research must be done to prove the efficacy of these treatments and make them widely available to those who have ASD.

Discussion

The present paper has synthesized current research on the causes, diagnosis, and treatment of Autism Spectrum Disorders. These are the areas seeming to require the most research and continued effort. The genetic causes are just beginning to be identified and could unlock pharmacological treatment for the core symptoms of ASD. Epigenetic and prenatal influences further complicate the etiology of the disease. The involved enviornmental factors are complex and should be investigated in preventative care, such as prenatal diet. Biological features of ASD should be noted, including brain structure and function, the action of the gut-brain axis, and their relation to the pathology of the disorder.

In general, diagnosis should be shifted from behavioral to biological criteria as soon as significant biomarkers can be identified and proven to generalize to the ASD population. Until then, the diagnostic process must consider the individual as a whole and researchers should persist in identifying potential biomarkers. The diagnostic and treatment processes must also consider the presence of comorbidities. Advancement should continue in developing treatments directed at common mechanisms of action behind ASD, such as microbial-based therapeutic interventions and behavioral interventions geared toward individual needs. Additionally, treatment should be collaborative and include a variety of therapeutic options including biological, behavioral, or pharmacological interventions.

Efforts to increase access to healthcare should be made for individuals of all ages who have ASD. Acceptance within the workforce and higher education should be increased with support in place for staff and students with ASD. Overall awareness and acceptance of ASD needs to increase, removing stigma from an individual's physical and mental healthcare.

Methodology

The present project is a literature synthesis detailing the causes, diagnosis, and treatment of autism, and future directions within these areas. This is accomplished through dutiful research, comprising current knowledge in the field. Databases that were used include PubMed, PsychINFO, and Google Scholar. Search terms included ASD, Autism Spectrum Disorders, autism, and topic specific items.

Current perspectives on the causes of ASD were discussed first, including relevant genetic and environmental factors. Information that is currently accepted on the etiology of the disorder was summarized. Next, the diagnostic criteria for ASD were presented and critically analyzed by cross-referencing current research in the area. Then, this paper detailed validated therapeutic, non-invasive, and pharmacological treatments for ASD. Last, promising future directions were addressed with the hopes of encouraging further research into ASD.

Conclusion

ASD is a prevalent neurodevelopmental disorder that impacts many facets of life for individuals who are affected. Considering the diverse causes and complicated pathology of ASD, research must investigate the genetic mechanisms involved and unravel the interaction of environmental factors. The heterogeneity between individuals on the spectrum presents a challenge in the diagnosis and treatment of ASD. Progress in the diagnostic process and criteria for ASD could allow for greater application of diagnostic tests to all populations and discrimination between those who have a confirmed diagnosis based on individual needs.

Biological aspects of the disease should be utilized in the diagnosis and treatment of ASD as soon as they are discovered and verified. Social advancement is needed to increase accessibility to all types of healthcare and promote involvement of individuals with ASD in school, work, and local communities. Treatment of ASD has been rapidly progressing, yet much research must be done to validate treatment options with the potential to help more individuals and reduce the experience of side effects. The coordination of numerous forms of treatment can also lend to individualization of treatment and a combination of interventions that will benefit the patient the most (based on their personal abilities, needs, and presentation). Many unanswered questions on the etiology and management of ASD leave room for knowledge and understanding to progress. Overall, ASD provides a wide array of research opportunities and advancement within these areas could have meaningful impacts on the lives of individuals who have ASD and their families.

Biographical Note

The author is an undergraduate student at Oakland University pursuing a bachelor's degree in biomedical sciences with a minor in psychology. She respects science for the exploration and answers it can provide, but her passion lies in helping others. Currently employed as an ABA (Applied Behavioral Analysis) technician, she plans to continue working in the field of psychology and providing services to vulnerable populations. While she absolutely adores children and may want to work with them in the future, the relationship between the brain and behavior piques her curiosity. She plans to further her education by attending graduate school and aspires to become a clinical neuropsychologist. In this role, she will be able to study

how physiology impacts behavior and gain clinical experience in neuropsychological assessment. The author hopes to work as a licensed clinical neuropsychologist and provide services to people in need.

The present project is of great interest to the author because she recognizes challenges faced by individuals who have developmental disabilities or psychological disorders. These disorders significantly impact many facets of life, such as social, emotional, behavioral, psychological, and physical well-being. Much more research must be done to better understand the causes of and treatments for autism spectrum disorders. In order to enact meaningful change in the lives of individuals who have autism, the scientific community and the general population have to learn how autism works and how best to accommodate individuals who are affected by it and their families. The author hopes to learn as much as possible about autism spectrum disorders and spread awareness. With this project, she hopes to contribute to advancing research in the area of autism spectrum disorders and benefit the scientific study of the brain and behavior.

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