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## Review Article

## Autism: A review

Chanchal S. Chandak<sup>1\*</sup>, Kiran P. Gaikwad<sup>1</sup>, Jaya P. Ambhore<sup>1</sup>, Vaibhav S. Adhao<sup>1</sup>,  
Raju R. Thenge<sup>1</sup>, Ritesh R. Popat<sup>1</sup>, Ashwini A. Zanke<sup>1</sup><sup>1</sup>Dept. of Pharmacy, Dr. Rajendra Gode College of Pharmacy, Malkapur, Maharashtra, India

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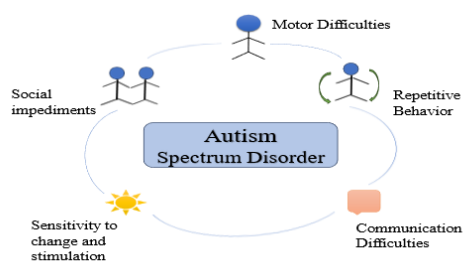
## ABSTRACT

Reduced eye contact, facial expressions, and body movements during the first three years of life are among the social behaviors and nonverbal interactions that define autism spectrum disorder (ASD), a collection of neurodevelopmental diseases. It is generally accepted that this condition is a multifactorial disorder resulting from the combination of both hereditary and non-genetic risk factors. It is not a single disorder. Studies on the genetics of ASD have found mutations that disrupt normal neurodevelopment from infancy through childhood. Axon mobility and synaptogenesis have been linked to these gene complexes. Advances in neuroimaging research have yielded numerous significant insights into the pathological alterations that take place in the brains of individuals with ASD while they are living their lives. Numerous neuropathological and neuroimaging studies have demonstrated the significance of the amygdala, a key component of the limbic system and the affective loop of the cortico-striatothalamo-cortical circuit, in cognition and ASD. The nucleus accumbens is seen as another important structure associated with the social reward response in ASD, in addition to the amygdala. While behavioral and educational interventions have traditionally been the cornerstones of ASD care, pharmaceutical and interventional therapies have also demonstrated some promise in ASD patients. Additionally, a small number of individuals have reportedly improved following deep brain stimulation, one of the interventional treatments.

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## 1. Introduction



\* Corresponding author.

E-mail address: [chanchalchandak1998@gmail.com](mailto:chanchalchandak1998@gmail.com) (C. S. Chandak).

A collection of neurodevelopmental diseases known as autism spectrum disorder (ASD) are defined by a deficiency in social interaction and verbal and nonverbal communication during the first three years of life. Avoiding eye contact, having difficulty controlling one's emotions or interpreting those of others, and having a noticeably narrow range of interests and activities are some examples of the characteristic social behaviors.<sup>1</sup> According to recent large-scale surveys, the prevalence of ASD is currently between 1% and 2%. Over the previous 20 years, ASD has become more common. An increase in risk variables cannot be ruled out, even though the DSM diagnostic criteria changes and earlier diagnosis age are partially to blame for the increase in prevalence. ASD affects men two to three times more frequently than it does women, according to studies.

It's possible that the underdiagnosis of females with ASD contributes to this diagnostic bias towards males.<sup>2,3</sup>

Furthermore, some researchers have raised the prospect that there may be female-specific protective effects against ASD. The word "autism" was first used in 1912 by Swiss psychiatrist Paul Eugen Bleuler to describe the symptoms of schizophrenia.<sup>4</sup> His source was the Greek term *autos*, meaning "self." In 1938, Hans Asperger used Bleuler's current definition of "autistic" to characterize the psychology of children. Later, he wrote about four boys who did not associate with their peers and who had no idea what it meant to be "polite," "respectful," or to show deference to an adult's authority. Additionally, the guys displayed distinct abnormal stereotypical behaviors. The pattern of behaviors that Asperger described as "autistic psychopathy" is today known as Asperger's syndrome. Leo Kanner is credited with coining the term "autism" in the contemporary sense. He coined the term "early infantile autism" in 1943 after reporting that around eight boys and three girls lacked "an innate inability to form the usual, biologically provided affective contact with people".<sup>5</sup> It is widely acknowledged that Leo Kanner and Hans Asperger laid the groundwork for the current field of autism research. As previously mentioned, the complex brain development of people with ASD is influenced by a variety of genetic, environmental, and interplaying factors. Studies on the genetics of ASD have found mutations that disrupt normal neurodevelopment from infancy through childhood. Axon mobility and synaptogenesis have been linked to these gene complexes. Additionally, as a result of these anomalies in the microstructural, macrostructural, and functional domains during brain development, a pattern of malformed neural networks pertaining to socioemotional processing is produced. Microstructurally, disarray of the cortical layers and a changed ratio of short-to long-diameter axons are seen. Macrostructurally, early brain development is typically characterized by cortical and subcortical grey matter enlargement, according to MRI studies measuring brain volume in people with ASD.

Functionally, research on resting-state functional magnetic resonance imaging (fMRI) reveals a story of global underconnectivity in socioemotional networks, whereas research on task-based fMRI reveals reduced activation of networks related to socioemotional processing. Furthermore, electrophysiological investigations show that patients with ASD have altered resting-state and stimulus-induced oscillatory activity.<sup>6</sup> ASD has been linked to conserved gene sets and genetic pathways, many of which are involved in the development, stability, and upkeep of functioning synapses. Consequently, these genetic components are crucial to understanding the pathophysiology of ASD, as is a thorough phenotypic examination of the cellular and behavioral traits. The number of genes linked to ASD that have already been

identified offers hope for using this knowledge to create novel therapeutic approaches. Important insights into the various aspects of human ASD are now being provided by basic research conducted in animal models. But more research is still required to fully comprehend the genetic, molecular, and circuit level abnormalities in ASD.<sup>7</sup> Numerous significant insights into the pathological alterations that take place in the brains of people with ASD in vivo have been gained from neuroimaging research. Crucially, an abnormal route of brain development associated with ASD results in variations in neuroanatomy, neurofunction, and connection. Despite significant advancements in the creation of animal models and cellular assays, neuroimaging techniques enable us to directly assess the brain in vivo and may help to create a more individualized treatment plan for ASD.<sup>8</sup>

## 2. Beginning of Autism

ASD is not a solitary illness. Nowadays, most people agree that it is a multifactorial condition caused by interacting hereditary and non-genetic risk factors. 10%–20% of people with ASD have chromosomal abnormalities and gene deficiencies, among other genetic reasons. Siblings born into families where there is an ASD subject are 50 times more likely to get ASD themselves, and the recurrence incidence is 5%–8%.<sup>9</sup> In monozygotic twins, the concordance rate can reach 82%–92%, but in dizygotic twins, it is only 1%–10%. Single gene mutations may change the developmental paths of neuronal and axonal structures involved in synaptogenesis, according to genetic research.<sup>10</sup> The most likely mechanisms in cases of tuberous sclerosis and fragile X syndrome are assumed to be aberrant neuronal synchronization and hyperexcitability of neocortical circuits brought on by changes in the neocortical excitatory/inhibitory balance.<sup>11</sup> Although it has not been completely determined, genome-wide linkage studies have revealed that susceptibility genes are located on chromosomes 2q,7q,15q, and 16p. The alteration of neuronal connections, brain growth, and synaptic/dendritic architecture have all been linked to these chromosomal anomalies.<sup>12,13</sup> Less than 5% of people with ASD also have metabolic abnormalities, such as phenylketonuria, creatine deficiency syndromes, adenyly succinate lyase deficiency, and metabolic purine disorders. It was recently revealed that autism and the cerebellum developmental patterning gene *ENGRAILED 2* were correlated. In as many as 40% of cases of ASD, it is the initial genetic variant that increases vulnerability to the disorder. Additional genes that have been proposed as hereditary determinants for ASD include the *UBE3A* locus, GABA system genes, and serotonin transporter genes. ASD is also caused by a variety of environmental factors, including as prenatal, perinatal, and postnatal variables.<sup>14</sup> Prenatal exposure to teratogens like thalidomide, certain viral infections (such as

congenital rubella syndrome), and maternal anticonvulsants like valproic acid are among the factors linked to ASD. The perinatal factors include low birth weight, excessively short gestation length, and birth hypoxia.<sup>15</sup> According to reports, autoimmune disorders, viral infections, hypoxia, mercury exposure, and other conditions are postnatal risk factors for ASD.<sup>16</sup>

### 3. Scientific Features and Examination of the Autism

#### 3.1. Scientific features

ASD is typically noticed in the first 3 years of life, with deficits in social behaviour and non-verbal interaction. Clinical features observed in children in different age of child are shown in Figure 1.<sup>17</sup>

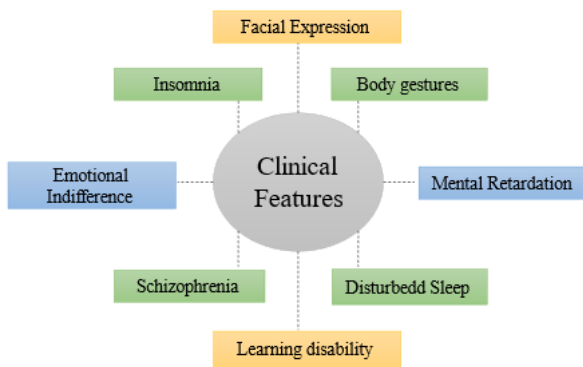


Figure 1: Clinical features of Autism

### 4. Analysis of the Disease

ASD is diagnosed clinically based on the presence of core symptoms. However, caution is required when diagnosing ASD because of non-specific manifestation in different age groups and individual abilities in intelligence and verbal domains. Diagnosis of ASD on the basis of age group is given in Figure 2, Figure 3 and Figure 4<sup>18</sup>

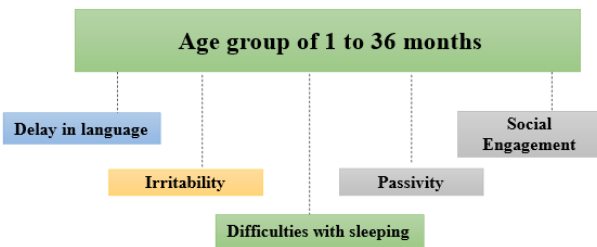


Figure 2: Analysis of disease in age group of 1 to 36 month

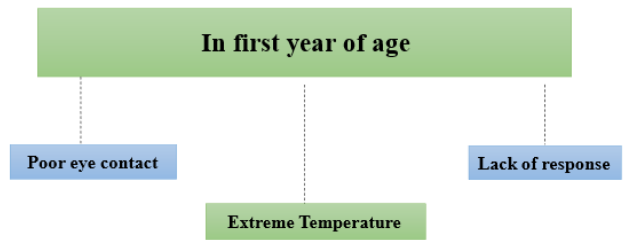


Figure 3: Analysis of disease in age group of first year of age

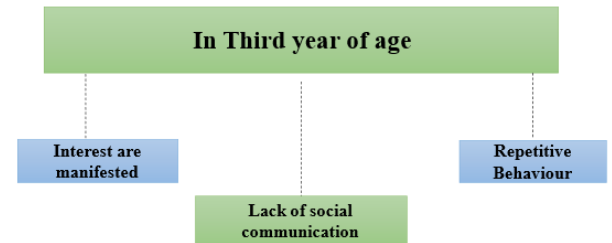


Figure 4: Analysis of disease in age group of third year of age

### 5. Relation of Amygdala (Part of brain) and ASD

The brain regions that are most noticeably damaged in people with ASD are the frontal and temporal lobes. More specifically, a number of neuropathological and neuroimaging investigations have demonstrated the significance of the amygdala in cognition and ASD. It has long been believed that social and aggressive behaviors in individuals with ASD are strongly correlated with the amygdala, which is situated in the medial temporal lobe anterior to the hippocampal formation.<sup>19</sup> A key element of the limbic system and the affective loop of the cortico-striatothalamo-cortical circuit is the amygdala.<sup>20</sup>

Two distinct functions of the amygdala are face processing and eye gazing. When the amygdala is damaged, fear is processed, memories containing emotional content are modulated, and people stare at faces with their eyes. The results in people with amygdala lesions are comparable to the ASD phenomena. High-processed somatosensory, visual, auditory, and visceral stimuli of various kinds are received by the amygdala. The ventral amygdalofugal pathway and the stria terminalis are the two main routes via which it sends efferents.<sup>21</sup>

There are thirteen nuclei in the amygdala. The basolateral (BL), centromedial (CM), and superficial groups are the three main groupings into which these 13 nuclei are separated based on histochemical investigations.<sup>22</sup> According to the BL group, the amygdala serves as a node that links sensory stimuli to a higher level of social cognition. It reciprocally connects the orbitofrontal cortex,

anterior cingulate cortex (ACC), and medial prefrontal cortex (mPFC) in addition to connecting the CM and superficial groups. The BL group of the amygdala differs from the other two groups in that its neurons are receptive to the faces and activities of other people.<sup>23</sup> The periamygdaloid complex, cortical, medial, and central nuclei make up the CM group. It supplies a significant output to the hypothalamus, thalamus, ventral tegmental area, and reticular formation in addition to innervating a large number of the brain stem's visceral and autonomic effector regions.<sup>24</sup> The lateral olfactory tract nucleus is a member of the superficial group.<sup>25</sup>

The amygdala has a significant number of opiate receptors and a high density of benzodiazepine/GABA<sub>A</sub> receptors, according to neurochemical investigations. In addition, it consists of noradrenergic, cholinergic, dopaminergic, and serotonergic cell bodies and pathways. The role of the amygdala in processing emotions, particularly rage, has been studied since bilateral stereotactic ablation of basal and corticomедial amygdaloid nuclei improved aggressive behavior in some patients with temporal epilepsy and aggressive behaviour.<sup>26</sup> There have been some theories regarding the amygdala deficiency in ASD patients. Compared to age- and sex-matched controls, postmortem investigations revealed dysfunction in the amygdala of people with ASD.<sup>27</sup> Patients with ASD were shown to have smaller neurons and higher cell density in the cortical, medial, and central amygdala nuclei.<sup>28</sup>

### 5.1. Relation of prefrontal cortex (Part of brain) and ASD

The frontal lobe is thought to be a crucial component of autism and to play a significant role in higher-level control. Higher-order cognitive, verbal, social, and emotional dysfunction is seen by those with frontal lobe deficiency, which is absent in autism. Recent research in neuropsychology and neuroimaging has tried to identify specific prefrontal cortex regions that support certain elements of executive function. According to certain writers, infants with ASD exhibit abnormally high rates of brain growth, primarily due to an increase in frontal cortex volume<sup>29</sup>. Particularly, the structure associated with ASD has been identified in the PFC, which includes Brodmann regions 8, 9, 10, 11, 44, 45, 46, and 47. The PFC is physically described as the areas of the cerebral cortex anterior to the premotor cortex and the supplementary motor area<sup>30</sup>, and cytoarchitectonically defined as the existence of a cortical granular layer IV. There are numerous connections between the PFC and other brain stem, cortical, and subcortical regions. It is fed information via the brainstem arousal systems, and its neurochemical environment has a major role in how well it functions.<sup>31</sup>

The PFC can be classified into two main categories: the lateral PFC (IPFC) and the medial PFC (mPFC).

The medial precentral cortex, anterior cingulate cortex, prelimbic and infralimbic prefrontal cortex are the four other regions that make up the mPFC. The mPFC contains reciprocal connections with brain regions involved in emotional processing (amygdala), memory (hippocampus), and higher-order sensory regions (within temporal cortex).<sup>32</sup> even though the IPFC is assumed to help the cognitive control process.<sup>33</sup> Given its role in social cognition and interaction, the mPFC may be an important area for comprehending oneself and other people.<sup>34</sup>

The mPFC and the basolateral amygdala have reciprocal synaptic connections that aid in the acquisition and extinction of fear. It is thought that the amygdala's output and related behavioral events are regulated and controlled by the mPFC.<sup>35</sup> Through functional disconnection, previous scientists examined how interconnections between BLA and mPFC govern memory processing. Impaired connection in the amygdala-mPFC circuitry led to memory processing deficiencies. These data lend credence to the involvement of the mPFC in the onset of ASD.

## 6. Relation of Nucleus Accumbens (Part of brain) and ASD

The nucleus accumbens (NAc), in addition to the amygdala, is thought to be the primary structure associated with the social reward response in ASD. The lateral subventricular fundus of the NAc is permeated in rostral sections by internal capsule fiber bundles, and the NAc borders the anterior limb of the internal capsule ventrally. Because of its prominent function in modifying the processing of reward and pleasure, NAc is a plausible candidate for DBS for ASD. The NAc and other limbic structures are recruited when rewarding stimuli are anticipated, and the NAc, the caudate, putamen, amygdala, and VMPFC are activated when pleasure is experienced.<sup>36</sup> It is commonly recognized that individuals with depression exhibit malfunctioning of the NAc in response to pleasant stimuli.<sup>37</sup>

### 6.1. Genetic factor which affects ASD

ASD is regarded as a highly heritable complicated genetic condition. The significant genetic component of ASD is shown by epidemiological twin research. For identical twins, the concordance rate is 70–90%, while for fraternal twins, it is 0–10%.<sup>38</sup> Familial clustering is seen in families where there are active cases of ASD. Younger male brothers are particularly more at risk for ASD than younger siblings of other family members who have received an ASD diagnosis.<sup>39</sup> Genetic variants, both common and unusual, and common polymorphisms associated with ASD can be identified as the etiology of 20–25% of ASD in children or adults.<sup>40</sup> About 1000 genes are linked to ASD overall in the SFARI (Simons Foundation autistic Research Initiative) gene database, which is a database of autistic candidate

genes. Genes added to the database are categorized into four groups: S syndromic, category 1, category 2, and category 3. The scores assigned to each gene are dependent on how strongly the gene is associated with the risk of ASD.<sup>41</sup> The 126 genes that are presently included in category S contain mutations that carry a significant risk for autism spectrum disorders (ASD) as well as extra traits that don't need to be present for a diagnosis of ASD. The function of genes in ASD is highly confidently predicted for those discovered in category 1. Their relevance to ASD is predicated on the existence, according to the literature, of three or more de novo mutations, their inclusion in the SPARK list<sup>42</sup>, and, in the majority of cases, a false discovery rate threshold of less than 0.1. There are currently 207 genes in category 1.

It is suggested that the 211 genes in category 2 are excellent candidates for a relationship with ASD. A strong candidate ASD gene requires the publication of at least two de novo mutations in the literature. A genome-wide significance threshold ( $p \leq 5 \times 10^{-8}$ ) or evidence of a functional effect of the mutation in a genome-wide association study (GWAS) should be present in the gene of interest. This threshold establishes the statistical significance of a reported association between a common variant and a given trait. Out of all the genes classified as suggestive candidates related with ASD, 506 genes are included in Category 3. There is only one known de novo mutation for these genes, or the gene has been linked to a GWAS that has not been established yet.<sup>43</sup>

## 6.2. Environmental factor which affects Autism

Parental age, the nutritional and metabolic health of the mother, prenatal infections, prenatal stress, and exposure to specific chemicals, heavy metals, or medications are examples of non-genetic factors that may moderate the risk of ASD. Genetic mutations may be influenced by the parents' ages. The risk of ASD in kids has been demonstrated to rise with increasing paternal age; however, some research has refuted this theory.<sup>44</sup> The nutritional health of the mother during pregnancy is essential for the appropriate development of the brain. Neurodevelopment may be hampered by an excess or a deficiency of micronutrients such as folic acid, zinc, iron, vitamin D, and omega-3. Comparative research has shown that children who grow up in folic acid-deficient environments have an increased risk of ASD.<sup>45</sup> On the other hand, neurocognitive deficits are also brought on by folic acid excess. ASD has been connected to trace metal dyschondrosteosis, which has also been demonstrated to impact brain development. Specifically, toxic metal buildup (lead, mercury) and zinc deficiency during pregnancy have been associated with autism spectrum disorders (ASD) in animal and epidemiological research.

Maternal infection is another non-genetic factor that raises the chance for ASD.<sup>46</sup> The relationship

between infections and immunological activation has been continuously examined since congenital rubella infections were linked to the development of ASD. The emphasis now is on the immunological response that an infection may cause in mothers, including cytokine activation and inflammation. Studies on maternal immune activation are being conducted using rhesus macaques and mice as animal models. Numerous theories have been put up regarding the possibility that maternal cytokines could transfer to the placenta, causing inflammation and excessive cytokine production in the developing embryo as well as potential gene dysregulation.<sup>47</sup> Studies on rhesus macaques including maternal antibody exposure have confirmed a shared endophenotype of ASD by means of maternal immune activation, which results in increased brain development and total cerebral volume in the offspring. According to numerous research, people with ASD have aberrant innate and adaptive immune systems, indicating that inflammatory disorders are not limited to pregnancy but rather last into adulthood. For example, increased amounts of chemokines and cytokines have been found in peripheral blood and the central nervous system.<sup>48,49</sup> Increased proinflammatory cytokine levels and the activation of microglia and astrocyte cells throughout life point to a neuroinflammatory profile in ASD that may be important in triggering ASD behaviour<sup>50</sup>

Pregnancy-related medication use by mothers, particularly for the treatment of depression and epilepsy, has been linked to an increased risk of ASD. Research has linked maternal valproate usage to a number of neurological changes in the offspring, including autism spectrum disorder (ASD); however, there are signs that the relationship may be dose-related. Pregnant women who use antidepressants, such as selective serotonin reuptake inhibitors, may be more likely to have ASD; nevertheless, mixed findings have also been reported.<sup>51</sup>

Maternal immune activation and prenatal zinc insufficiency have been modeled in animals and identified as possibly causal factors; the underlying mechanisms have been examined, even though the majority of the data on paternal factors are based on epidemiological research. Furthermore, a number of environmental variables, such as obesity, epilepsy, and gastrointestinal diseases, raise the incidence of co-morbidities.<sup>52</sup>

## 7. Management of Autism

The foundation of ASD management has been a variety of behavioral and educational interventions. Individualized treatment is recommended for ASD, according to the majority of doctors. Educational and behavioral interventions may continue more smoothly if incapacitating symptoms like hostility, agitation, hyperactivity, inattention, impatience, and repetitive and self-injurious conduct are treated.<sup>53</sup>

The role of different pharmacological treatments is gaining more attention. Typical and atypical antipsychotics, antidepressants, selective serotonin reuptake inhibitors,  $\alpha$ 2-adrenergic agonists,  $\beta$ -adrenergic antagonists, mood stabilizers, and anticonvulsants are among the medications used in medical therapy. As of yet, no agent has been shown to be successful in social communication. Knowledge of particular individual medical, behavioral, or psychiatric problems coexisting with ASD, such as obsessive-compulsive disorder, schizophrenia, mood disorder, and intellectual disability, has a significant role in the choice of pharmacologic treatment.<sup>54</sup>

The most often utilized medications were antidepressants, which were followed by stimulants and antipsychotics. The rates of psychotropic medication use among individuals with ASD are indicative of a high frequency of comorbidities. Antipsychotics were useful in treating children with ASD for their repetitive behaviors, but there was insufficient data to determine their safety and effectiveness in treating adults and adolescents with ASD. Opiate antagonists, immunotherapy, hormonal medicines, megavitamins, and other dietary supplements are some more alternatives.

Nonetheless, some patients' autistic symptoms continue to be unresponsive to pharmacological therapy. These people's quality of life has been negatively impacted by their numerous comorbidities and severely advanced disease. For these patients, another therapeutic option could be interventional therapy, such as deep brain stimulation (DBS).

Focused intervention techniques and comprehensive treatments are the two types of interventions that have been employed to treat ASD. Prompting, reinforcement, discrete trial instruction, social tales, or peer-mediated interventions are examples of targeted intervention techniques. These are employed for a brief period of time with the aim of demonstrating a change in the targeted behaviors, and they are made to achieve certain behavioral or developmental results for individual children with ASD. The comprehensive therapy models consist of a series of activities that are applied intensely over a prolonged period of time and typically involve several components.

DBS has been utilized to deliver electrical impulses to particular brain regions since the FDA approved it in 1997. The range of conditions for which DBS is therapeutically beneficial has significantly broadened recently, encompassing not just psychiatric illnesses but also movement disorders such as essential tremor, Parkinson's disease, and dystonia. For the past few years, some writers have shown the effectiveness of DBS for treating psychiatric diseases such as depression, Tourette syndrome, refractory obsessive-compulsive disorder, and others.<sup>55</sup>

## 8. Conclusion

Due to intricate underlying pathomechanisms that are activated by a variety of events, ASD are quite

heterogeneous. Numerous studies have provided additional evidence for the involvement of the amygdala and NA in the pathophysiology of ASD. It has multiple etiologies that involve both hereditary and environmental factors. While some adults and children with ASD are completely capable of carrying out all everyday tasks, others need a lot of assistance to even do the most basic tasks. The pathogenic processes and etiology are still not fully understood. The majority of people with ASD have a fundamental illness, nevertheless, which is hinted at by the presence of common behavioural traits that serve as the basis for the diagnosis of the disorder. Since ASD is linked to a significant socioeconomic burden, further study into the etiology and pathology of ASD is required in order to find potential biomarkers, develop preventative and treatment plans, and enhance already available medications. People with ASD will greatly benefit from a tailored medical approach due to the significant degree of heterogeneity.

## 9. Abbreviations

1. ASD - Autism spectrum disorder
2. DBS - Deep Brain Stimulation
3. GWAS - Genome-Wide Association Study
4. BL- Basolateral
5. CM – Centromedial

## 10. Source of Funding

None.

## 11. Conflicts of Interest

The authors declared no potential conflicts of interest

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## Author biography

**Chanchal S. Chandak**, Assistant Professor  <https://orcid.org/0009-0007-2627-1596>

**Kiran P. Gaikwad**, Assistant Professor

**Jaya P. Ambhore**, Assistant Professor

**Vaibhav S. Adhao**, Professor

**Raju R. Thenge**, Associate Professor

**Ritesh R. Popat**, Associate Professor

**Ashwini A. Zanke**, Assistant Professor

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