Iran J Psychiatry 2026; 21: 1: 129-139

Review Article ***https://doi.org/10.18502/ijps.v21i1.20570***

Autism and Human Papillomavirus (HPV) E6: A Comprehensive Review

Najmeh Sheikhi[1], Faezeh Hajizadeh[1], Jamal Sarvari[2], Zahra Bazi[3], Iliad Moradi[4], Abdolvahab Moradi[1*]

Abstract

Objective: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social communication impairments, restricted interests, and repetitive behaviors. The etiology of ASD is complex, involving genetic and environmental factors. The HECT (Homologous to the E6-AP Carboxyl Terminus) family protein E6-associated protein (E6-AP), encoded by the UBE3A gene, is an ubiquitin ligase implicated in neurological disorders, including Angelman syndrome (AS) and potentially ASD. Dysregulation of E6-AP, influenced by environmental factors such as human papillomavirus (HPV) E6 protein, may contribute to neurodevelopmental abnormalities.
Method: This review synthesizes current literature to explore the potential link between HPV E6 protein and E6-AP dysfunction in the context of ASD. We analyzed 32 peer-reviewed studies, including 12 original research articles, 10 reviews, and 10 meta-analyses, retrieved from PubMed and Google Scholar, focusing on E6-AP's roles in ubiquitin-mediated signaling pathways, its dysregulation in neurodevelopmental disorders, and the impact of HPV E6 on E6-AP function.
Results: E6-AP is critical in regulating signaling pathways associated with tumorigenesis and neurodevelopment. Dysregulation of E6-AP, potentially induced by HPV E6, has been implicated in AS and, to a lesser extent, ASD. As visually demonstrated in Figure 1, these complex relationships between HPV, neurodevelopmental disorders, and E6 protein underscore the need for cross-disciplinary research. Current findings indicate that HPV E6 may disrupt E6-AP's ubiquitin ligase activity, potentially contributing to neurodevelopmental impairments observed in ASD.
Conclusion: The potential link between HPV E6 and E6-AP dysfunction underscores a novel avenue for understanding environmental contributors to ASD. Given the complexity of ASD, further research is essential to elucidate E6-AP's role and to develop targeted therapeutic strategies. This review highlights the need for studies investigating HPV-related mechanisms in ASD to advance effective interventions and support systems.

Key words: *Autism Spectrum Disorder; E6-Associated Protein (E6-AP); E6 Protein; Human Papillomavirus (HPV)*

1. Department of Microbiology, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran.
2. Department of Bacteriology and Virology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
3. Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Golestan University of Medical Sciences, Gorgan, Iran.
4. Department of Laboratory Sciences, School of Allied Medical Sciences, Iran University of Medical Sciences, Tehran, Iran.

***Corresponding Author:**
Address: Department of Microbiology, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran, Postal Code: 4934174515.
Tel: 98- 911 1772107, Email: dr.moradi@goums.ac.ir

Article Information:
Received Date: 2025/05/17, Revised Date: 2025/08/25, Accepted Date: 2025/10/26

Copyright © 2026 Tehran University of Medical Sciences. Published by Tehran University of Medical Sciences.
This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license (https://creativecommons.org/licenses/by-nc/4.0/). Noncommercial uses of the work are permitted, provided the original work is properly cited

The E6 protein, encoded by high-risk human papillomavirus (HPV) types, is a key oncoprotein that plays a crucial role in HPV-associated carcinogenesis (1). E6 interacts with the ubiquitin ligase E6-associated protein (E6-AP or UBE3A), a protein that regulates diverse cellular processes, including the degradation of the tumor suppressor p53 (2-4). This interaction leads to the degradation of p53, promoting cell proliferation and tumor development (3). However, the precise mechanisms by which E6 and E6-AP interact and the consequences of this interaction for cellular function remain poorly understood (5, 6). The E6 protein of HPV, known to play a role in the oncogenic pathway of cervical cancer, may also contribute to neurodevelopmental anomalies through mechanisms not well documented in the existing literature (7). Autism spectrum disorder is a neurodevelopmental disorder characterized by social communication impairments, restricted interests, and repetitive behaviors (8). the disorder is a developmental disorder affecting brain development, hindering communication, social interaction, and play (9). A national study in Iran reported a 0.1% prevalence of the disorder in children and adolescents aged 6-18, with 86% having at least one comorbidity, including intellectual disability and epilepsy (10). While the exact causes of the disorder are complex and multifaceted, environmental factors are believed to play a significant role (8). Interestingly, E6-AP is also linked to the disorder, suggesting a potential connection between HPV and this neurodevelopmental disorder (2, 11, 12). E6-AP is an E3 ubiquitin ligase that regulate many cellular processes, including control of key neuronal signaling pathways, synaptic plasticity, dendritic spine maturation, and neuronal protein synthesis, by targeting specific substrates to be degraded by the proteasome (9). Disruption of E6-AP regulation of these processes alters electrophysiological connectivity in neurons, resulting in disrupted neuronal connectivity and operation, which is a key determinant of the disorder pathophysiology (13). E6-AP, as an example, regulates the presence of proteins that modify de novo formation and maturation of synapses, including Arc and Ephexin5. Malfunctioning of these pathways affected by E6-AP activity changes can thus be detrimental to neurodevelopment and cause ASD-related phenotypes (2). Further, the route is more probable since the heparan sulfate receptor is already considered a general receptor through which the virus can access cells of the nervous system (14).

By pursuing this line, we fulfill the existing scientific niches in neuroscience and virology and pose questions for better comprehension of potential etiological factors in ASD (15). The significance of this review lies in its potential to uncover new perspectives on how viral infections, particularly HPV, may contribute to neurodevelopmental outcomes and possibly to the etiology of disorders such as the disorder (16).

However, even though there is increasing evidence suggesting that E6-AP dysregulation and mutation are associated with neurological disorders, little is known regarding the underlying molecular mechanisms through which HPV E6 can manipulate the E6-AP in neural development (17). The gap in staining the neural tissues and the indirect systemic influences on directly affecting the neural processes of E6-AP is extensive. In addition, the interactions of E6-AP with additional neural regulators and signaling cascades associated with the disorder have not been investigated thoroughly and therefore need to be filled in this body of knowledge (18). Given the increasing prevalence of the disorder, understanding viral contributions could lead to enhanced prevention strategies and therapeutic interventions (19). The primary goals of this literature review are to synthesize existing studies on the interaction between HPV E6 protein and neurodevelopment, specifically regarding the disorder, and to evaluate the mechanisms underlying any observed associations (19). The scope of this review will encompass empirical studies solely focused on the relationship between HPV and the disorder, the biological roles of E6 in neurodevelopment, and possible implications for public health strategies (20). Mechanistic insights into how E6 may interact with cellular pathways relevant to neurodevelopment, and how such interactions could contribute to the disorder, will also be highlighted (21). This literature review will be organized as follows: the next section outlines the literature search strategy for collecting relevant studies, followed by background information on ASD and HPV. The review will conclude with a discussion of the findings' implications, existing knowledge gaps, and directions for future research. This review seeks to lay the groundwork for future investigations into the potential contributions of viral agents to neurodevelopmental disorders, fostering progress in this evolving area of research.

Materials and Methods

Research on the relationship between HPV and ASD is limited but includes diverse studies. This research conducted a comprehensive analysis of maternal HPV infection and its potential impact on neurodevelopmental disorders in offspring. Data were collected from medical records, patient interviews, and laboratory tests. Statistical methods from related articles were applied to evaluate the association between maternal HPV infection and neurodevelopmental outcomes in children. Some of the findings highlighted here are based on articles and research publications retrieved from Google Scholar and PubMed. To identify specific articles more precisely, we conducted a thorough search in the following databases, PubMed and Google Scholar with such keywords as HPV, ASD, maternal HPV infection, and neurodevelopment. Articles published up to 2025 were considered. The main inclusion criteria included original research studies, reviews, and meta-analyses in which

authors spoke of a biological or epidemiological connection between HPV and the disorder or other neurodevelopmental disorders. It has been reported that this protein is of importance as the alteration in ubiquitination processes controlled by E6-AP can be associated with different physiological diseases, including the disorder or other neurodevelopmental disorders. The non-English language papers, studies with no primary data on HPV-ASD associations, and articles outside of neurodevelopment were excluded. The method of selection consisted of screening of titles and abstracts, and full-text examination of importance and goodness. Structured tables were obtained by extraction of key data. The reviewed evidence was synergized in qualitative terms with an emphasis on putative molecular mechanisms, epidemiological conclusions, and therapeutic opportunities.

Mapping HPV E6–Human Protein Interactions Using IntAct and BioGRID Databases

To elucidate the potential influence of HPV E6 on autism, we evaluate the protein interactions with human proteins as cataloged in the IntAct and BioGRID databases. IntAct (Figure 2) and BioGRID (Figure 3) serve as invaluable resources for scholars engaged in the investigation of protein interactions and the delineation of molecular networks. IntAct is characterized by its rigorous experimental annotation and its commitment to open-source flexibility. Concurrently, BioGRID provides extensive coverage across various species, encompassing both genetic and chemical interactions while concentrating on biomedical applications and the integration of large-scale data. To ascertain pathways that exhibit statistical overrepresentation in proteins interacting with HPV E6, the EnrichR server was employed. Table 1 illustrates the pathway that was enriched in the human protein derived from the IntAct database. EnrichR represents a robust, web-based tool for gene set enrichment analysis, specifically designed to assist researchers in the interpretation of gene lists generated from genome-wide profiling endeavors. Database-to-database conversions (DB2DB) facilitated the identification of diseases associated with these genes.

Table 1. The Pathway that Was Enriched in the Human Protein Derived from the IntAct Database

Term	Overlap	Adjusted P-value	Combined Score
Human papillomavirus	17/331	2.03E-15	1086.572
Human T-cell leukemia virus 1 infection	12/219	4.81E-11	747.2803
Hepatitis B	10/162	6.69E-10	713.3953
Viral carcinogenesis	11/203	3.66E-10	659.6554
Cell cycle	8/124	3.58E-08	588.2578
Human cytomegalovirus infection	11/225	6.69E-10	565.4909
Kaposi sarcoma-associated herpesvirus infection	10/193	2.80E-09	550.0201

Overview of Autism Spectrum Disorder and Human Papillomavirus

This review explores the potential effects of maternal HPV infection on the neurodevelopment of offspring, including its associations with neurodevelopmental disorders such as ASD. It discusses the hypothesis that maternal immune responses and HPV infection during pregnancy may contribute to altered neurodevelopmental trajectories in children (19, 22). Characterized by a diverse range of symptoms affecting communication, behavior, and social interaction, ASD presents significant challenges for individuals and their families (23). The diagnosis typically occurs in early childhood, with varying degrees of severity and manifestations, leading to a spectrum of experiences among those affected (24). Current literature highlights a complex interaction of genetic, environmental, and neurodevelopmental factors in the etiology of the disorder, underscoring the importance of a multidisciplinary approach. (25). One emerging area of interest involves exploring the potential links between viral infections and neurodevelopmental disorders, where HPV has garnered attention due to its ubiquity and association with various health complications, particularly in immunocompromised populations (26). By examining these interactions, researchers seek to reveal mechanisms that explain the complex relationships between viral infections and neurodevelopment, ultimately improving diagnostic and therapeutic strategies for autism.

Study on Maternal HPV Infection and ADHD/ASD

A recent study aimed to look for a correlation between maternal HPV positivity and the development of ADHD or ASD in children (22). Data from the Taiwan National Health Insurance Research Database indicated that the offspring of mothers with HPV infection had a higher risk of developing ADHD, which was higher than the control group (27). Interestingly, this association was consistent with the time of HPV infection, before or during pregnancy. However, no significant association of risk involving the index group for the control group was noted for the disorder (28).

A significant study proposed that placental infection of HPV could be linked to the disorder based on various observations (29). The study mentioned that the concordance rate for the disorder in identical twins is not

absolute, implying an environmental factor, such as HPV infection, that may contribute to autism spectrum disorder. It highlighted the role of HPV in epigenetic changes and gene expression alterations in offspring that could lead to the disorder (28).

E6-Associated Protein (UBE3A) and Autism Spectrum Disorder

E6-AP is encoded by the UBE3A gene, which is located on chromosome 15q (2). Mutations in UBE3A, including deletions, are known to cause Angelman syndrome, a neurodevelopmental disorder characterized by severe intellectual disability, seizures, and movement disorders (2, 30, 31). Furthermore, increased dosage of UBE3A has been linked to increased penetrance of ASD, suggesting that the expression levels of E6-AP must be tightly regulated during brain development (2). E6-AP/UBE3A plays a role in the UPS pathway, and its disruption can stem from mutations in UBE3A or related genes associated with the disorder. Deletion of the HLH-3 ubiquitin ligase, likely disrupted by the HPV E6 oncoprotein, may result in the accumulation of specific substrates, potentially affecting neurodevelopmental processes linked to ASD (28, 32). E6-AP is also significant in the context of neurodevelopmental disorders. Mutations or dysregulation of the UBE3A gene, which encodes the E6-AP protein, have been implicated in Angelman syndrome and are also associated with certain cases of autism spectrum disorder (3). E6-AP overexpression is associated with some cases of the disorder. The HPV E6 protein interacts with E6-AP, resulting in the degradation of the tumor suppressor protein p53, which is essential in HPV-related cancers. This connection underscores E6-AP's dual role in neurodevelopmental disorders like the disorder and the progression of HPV-related cancers (5).

The precise mechanisms by which E6-AP dysregulation contributes to ASD are not fully understood. However, studies have suggested that E6-AP plays a role in various cellular processes crucial for brain development, including:

a. Neural stem cell proliferation, migration, and differentiation: E6-AP has been shown to influence the proliferation, migration, and differentiation of neural stem cells in the developing brain (8). This suggests that E6-AP dysregulation could disrupt these processes, leading to abnormal brain development and the disorder (9).
b. Synaptic plasticity and function: E6-AP has been implicated in the regulation of synaptic proteins, such as Arc, which is involved in synaptic plasticity (8). Prenatal viral infections, particularly maternal influenza, have been associated with an increased risk of schizophrenia and other neurodevelopmental disorders, potentially due to immune-mediated disruptions in fetal brain development. (33). These infections can initiate immune responses that lead to neuroinflammation, exacerbating neurodevelopmental vulnerabilities. Notably, chronic inflammation can impair synaptic plasticity, which is essential for learning and social functioning, often seen in autism (34). In synaptic plasticity, for example, the E6-AP gene has been implicated in multiple neurodevelopmental disorders such as the disorder (2).
c. Wnt signaling pathway: E6-AP has been demonstrated to interact with the proteasome, a cellular machinery responsible for protein degradation (25). This interaction is crucial for regulating the Wnt signaling pathway, which plays a role in brain development and neural stem cell proliferation (25). Mutations in the AZUL domain of E6-AP, associated with Angelman syndrome, can impair its interaction with the proteasome and disrupt Wnt signaling (25). Targeting specific receptors through therapeutic interventions may help alleviate cognitive and behavioral deficits (35). Ube3A/E6-AP functionality, the actions of HPV E6 proteins, and their influence on the normal E6-AP function may be implicated in these pathologic states. In other words, the E6 protein of HPV binds to E6-AP, a cancer-associated molecule especially related to cancer-related development and neurodevelopmental disorders like some forms of the disorder (36).
d. Nitric Oxide Pathway, the nitric oxide pathway has been implicated in the neurodevelopmental aspects of autism. Modulation of this pathway may help to alleviate some of the behavioral alterations seen in autistic individuals (37).
e. Calcium-Stimulated Adenylyl Cyclases: These enzymes have been identified as potential therapeutic targets for addressing aberrations in calcium signaling pathways associated with neurodevelopmental disorders. Such interventions may enhance the signaling processes critical for normal neuronal function (38).
f. Network Pharmacology Approaches: Utilizing network pharmacology to identify and target multiple pathways simultaneously may allow for comprehensive treatment strategies. These approaches could leverage interactions between E6-AP and various signaling pathways involved in the disorder (39).

The Role of Human Papillomavirus E6 in Autism Spectrum Disorder

While HPV infection is primarily associated with cancers, particularly cervical cancer, there is growing interest in exploring potential links between HPV and neurodevelopmental disorders (8). This interest stems from the fact that E6-AP, a key target of the HPV E6 oncoprotein, is also implicated in ASD (2, 30). E6-AP is also significant in the context of neurodevelopmental disorders, as mutations or dysregulation of E6-AP are linked to Angelman Syndrome, a neurodevelopmental disorder, and some cases of autism spectrum disorders (3). Overexpression of E6-AP has been linked to some cases of the disorder (13). The E6 protein from HPV interacts with E6-AP, leading to the degradation of the tumor suppressor protein p53, which is crucial in HPV-

associated cancers (40). This connection highlights the dual role of E6-AP in neurodevelopmental disorders such as the disorder and in the progression of HPV-related cancers (5, 11). The actions of HPV E6 proteins and E6-AP that influence the normal functions of E6-AP may play a role in these pathologic states. In other words, the E6 protein of HPV binds to E6-AP, a molecule related to cancerous growth and neurodevelopmental disorders such as certain types of autism (41).

a. E6-mediated degradation of p53: E6 interacts with E6-AP to promote the degradation of p53, a tumor suppressor protein that plays a role in cell cycle regulation and apoptosis (42). Although this interaction is well known to promote cancer development, E6 could potentially affect normal brain development by degrading p53, which may play a role in the development of ASD (43). As far as its biology is concerned, HPV oncoproteins are E6 and E7; importantly, E6 promotes the degradation of p53 (and time-permitted Rb) (44). This supports cell survival or proliferation because, when it occurs within infected cells, it changes their behavior towards uncontrolled growth and increases mutation rates relevant to cancer development (45). It has been reported that this protein is of importance as the alteration in ubiquitination processes controlled by E6-AP can be associated with different physiological diseases, including the disorder (46).
b. E6-induced dysregulation of E6-AP: E6 could directly or indirectly influence the activity and function of E6-AP (47). This could lead to dysregulation of E6-AP-dependent cellular processes, potentially impacting brain development and contributing to ASD (9).
c. E6-mediated disruption of neural stem cell function: E6 could directly or indirectly influence the multiplication, mobility, or differentiation of neural stem cells causing part of disturbed brain development and the disorder (8). The authors supply data regarding the connection between the UBE3A gene encoding the ubiquitin ligase E6-AP mutant and various comorbid neurodevelopmental disorders; additionally, the HPV oncoprotein E6 inactivates the UBE3A gene product (17, 48). E6-AP is associated with the neurodevelopmental disorder Angelman syndrome which presents features similar to autism. This implies that dysregulation which may be caused by HPV E6 oncoprotein might affect other diseases such as ASD (49).

Viral Pathogenesis Theories in Neurodevelopment

Other theories of viral pathogenesis propose that illness during critical stages in children's brain formation could lead to such disorders as autism (19). The neurodevelopmental hypothesis posits that certain viruses can impact brain development by causing direct damage or triggering immune responses that interfere with normal neurodevelopmental processes (50). HPV E6 proteins modulate the activity of E6-AP. Lack of E6-AP leads to Angelman Syndrome, while high expression of E6-AP is connected with ASDs (50). For instance, they may be useful in preventing the activity of the E6 oncoprotein through which compounds could assist in getting the regulatory proteins including p53 back to their proper functioning in growth control and other apoptotic abilities (51). Related molecular mechanisms of these natural inhibitors with E6 oncoprotein are well described within the scope of this research, suggesting the ability of the molecules to support the normal activities of E6-AP, p53, and Myc. Several compounds, including Ginkgetin, Hypericin, and Apigetrin, are considered to be the most potent inhibitors, with superior bindings to the E6-AP, p53 and Myc binding sites to the HPV16 E6 (52).

Rubella virus is associated with congenital rubella syndrome that leads to several developmental disabilities, such as including the disorder. Another terminal virus that may be contracted during pregnancy is cytomegalovirus (CMV), which affects fetal brain development, and the probability of autism increases. Furthermore, there are studies on maternal influenza infection during pregnancy, herpes simplex virus, varicella-zoster virus, and Zika virus; they have the potential to raise the odds of including the disorder (19, 53). We have previously examined the link between mental disorders and viruses in our study, "Low Prevalence of Borna Disease Virus RNA in Patients with Bipolar Major Depression and Schizophrenia in Northern Iran"(54).

Potential Drug Development

This study raises the molecules with the natural propensity to quell HPV E6 and E7 proteins vital for treating cervical cancer. This could result in the evolution of new effective drugs as well as from comparing the different enzymes and their mechanisms of catalysis (55).

Among 59 human proteins interacting with HPV16 E6 in the IntAct (Figure 2) database, UBE3A (an ubiquitin ligase), RPL10, MCM7, and TSC2 from db2db show associations with Autistic Disorder. Additionally, analysis of 162 genes in BioGRID (Figure 3) identifies 15 proteins linked to Autistic Disorder, including UBE3A, DLG4, MPDZ, SNTG2, TJP1, NOTCH1, ALDH3A2, CBR1, GTF2I, ITPR3, SLC3A2, TJP2, TSC2, KDM5C, and MYO1D. These findings (Tables 1 and 2) highlight potential molecular overlaps between HPV16 E6 interactions and neurodevelopmental pathways.

Key Findings from Recent Research

a. Gastrointestinal Symptoms: the research also established that gastrointestinal (GI) complaints are reported by children with ASD and are related to impairments in both social and adaptive functioning. While this study doesn't solely focus on E6-AP, understanding how gut health is linked to neurodevelopment further provides insight into what E6-AP influences in cellular health (56).

b. Neuroinflammation and Pathogenesis: Studies into neuroinflammatory and oxidative stress markers suggest that both of these factors play a major role in the manifestation of including the disorder. These pathways could be essential for E6-AP to regulate and may suggest that its altered regulation might lead to further neuroinflammation responsible for behavioral symptoms (57).
c. Microbiota-Gut-Brain Axis: Research discusses entrainment and its possible link to autism and gives stress to the relation between the gut and brain. In considering these issues, neurochemical pathways influenced by E6-AP may complement dietary factors and microbiota content altering metabolic and inflammatory pathways to influence the symptoms of the disorder (21, 58).
d. Screen Time Management and Digital Interventions:

Research Gaps and Future Directions

Despite the potential link between HPV E6 and ASD, research in this area is still in its early stages. Several key research gaps need to be addressed:

Direct evidence of HPV infection in individuals with ASD: Studies are needed to determine if HPV infection is more prevalent in individuals with the disorder compared to the general population.

Mechanisms of HPV E6 action in the brain: Further research is required to elucidate the specific mechanisms by which HPV E6 could influence brain development and ASD.

Clinical implications: Understanding the potential link between HPV E6 and ASD could affect clinical management and treatment strategies.

Key Findings from Recent Research

a. Gastrointestinal Symptoms: the research also established that gastrointestinal (GI) complaints are reported by children with ASD and are related to impairments in both social and adaptive functioning. While this study doesn't solely focus on E6-AP, understanding how gut health is linked to neurodevelopment further provides insight into what E6-AP influences in cellular health (56).
b. **Neuroinflammation and Pathogenesis:** Studies into neuroinflammatory and oxidative stress markers suggest that both of these factors play a major role in the manifestation of including the disorder. These pathways could be essential for E6-AP to regulate and may suggest that its altered regulation might lead to further neuroinflammation responsible for behavioral symptoms (57).
c. **Microbiota-Gut-Brain Axis:** Research discusses entrainment and its possible link to autism and gives stress to the relation between the gut and brain. In considering these issues, neurochemical pathways influenced by E6-AP may complement dietary factors and microbiota content altering metabolic and inflammatory pathways to influence the symptoms of the disorder (21, 58).
d. Screen Time Management and Digital Interventions:

Research Gaps and Future Directions

Despite the potential link between HPV E6 and ASD, research in this area is still in its early stages. Several key research gaps need to be addressed:

Direct evidence of HPV infection in individuals with ASD: Studies are needed to determine if HPV infection is more prevalent in individuals with the disorder compared to the general population.

Mechanisms of HPV E6 action in the brain: Further research is required to elucidate the specific mechanisms by which HPV E6 could influence brain development and ASD.

Clinical implications: Understanding the potential link between HPV E6 and ASD could affect clinical management and treatment strategies.

Table 2. The Pathway that Was Enriched in the Human Protein Derived from the BioGRID Database

Term	Overlap	Adjusted P-value	Combined Score
Proteasome	23/46	1.37E-25	3483.163
Spinocerebellar ataxia	25/143	1.81E-15	451.2207
Ubiquitin mediated proteolysis	24/140	9.58E-15	417.0161
Epstein-Barr virus infection	29/202	1.81E-15	363.6258
Parkinson disease	27/249	1.14E-11	196.5237
Human papillomavirus infection	29/331	2.67E-10	137.5618
Huntington disease	27/306	1.06E-09	129.7781
Prion disease	24/273	1.07E-08	114.4133
Alzheimer disease	28/369	1.07E-08	97.95817

Figure 1. This Diagram Depicts the Complex Relationships between Human Papillomavirus (HPV), Neurodevelopmental Disorders, and the Influence of the E6 Protein. It Emphasizes the need for cross-disciplinary research to clarify HPV's role in conditions such as Autism Spectrum Disorder (ASD) and the existing research limitations.

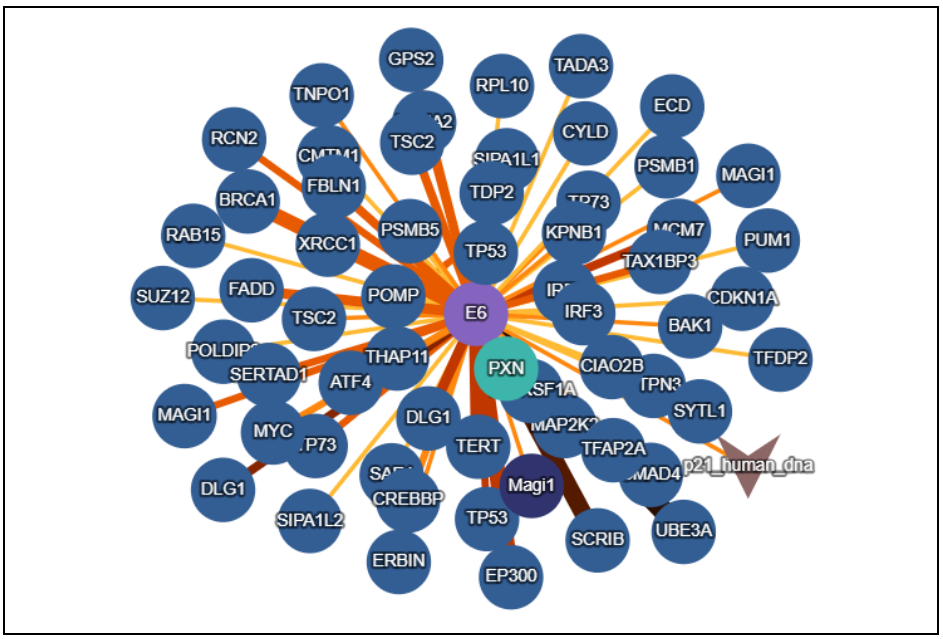

Figure 2. IntAct Database: HPV16 E6 (Central Purple Node) Interacts with ♁9 Human Proteins (Light Blue Nodes), 1 Murine Protein (Dark Blue Node), 1 Avian Protein (Green Node), and Human p21 DNA Sequence (Pink Downward Arrow)

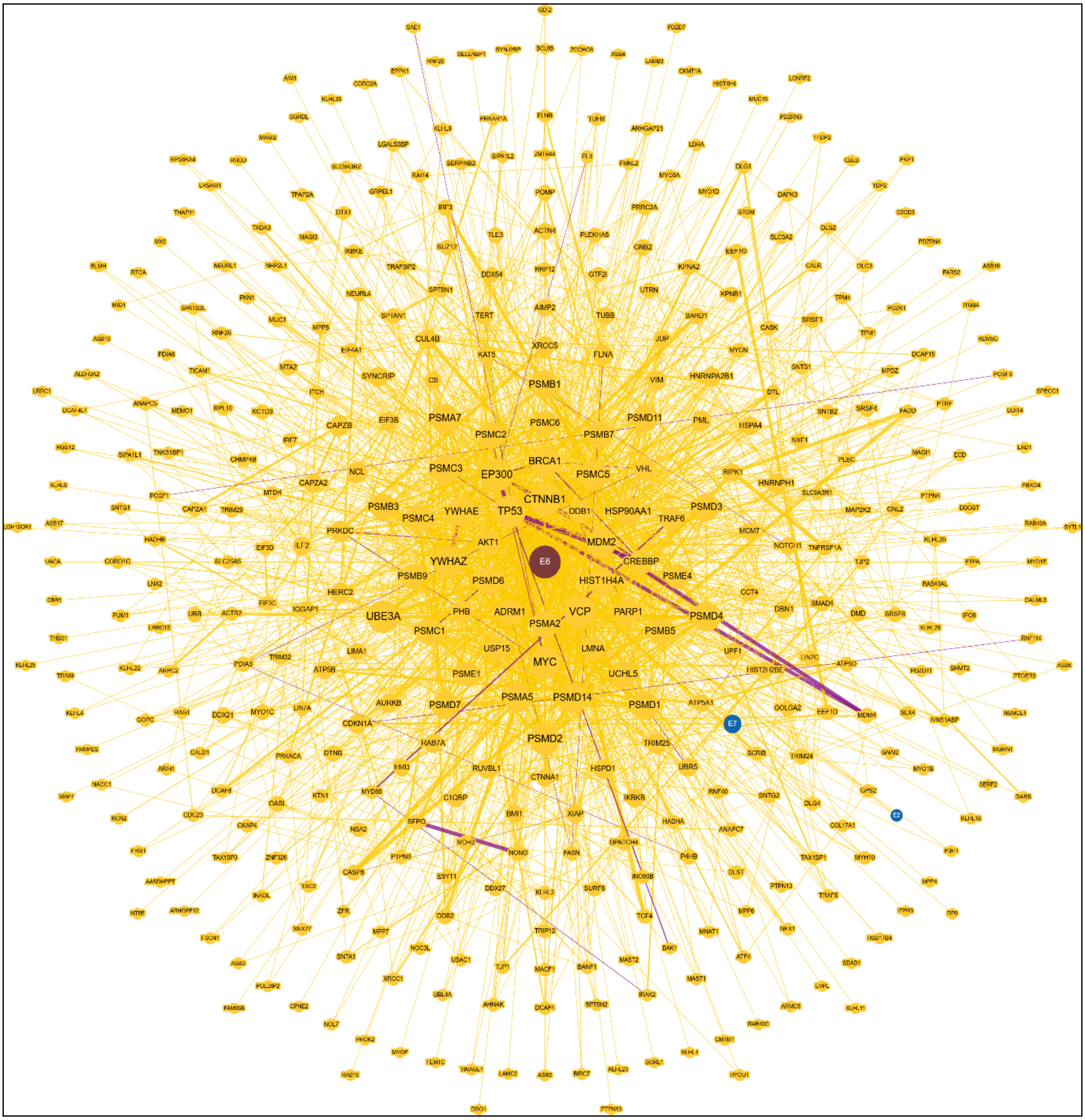

Figure 3. BioGRID Database: Human Papillomavirus 16 E6 (Central Purple Node) Interacts with 162 Human Proteins (Yellow Nodes)

Limitation

This review has several limitations that are to be listed. In the first place, literature in the usage of HPV in neurodevelopment and ASD is limited and most of the studies are still exploratory or preliminary. No large-scale epidemiologic data exist as to whether maternal or early-life HPV infection is directly related to a risk of the disorder. Second, viral contributions are difficult to isolate in the heterogeneous ASD and complex multifactorial etiology. Third, numerous mechanistic understandings are based on in vitro/animal models and are not perfectly transferable to a human context. Fourth, the publication bias and the language restrictions might restrain the spectrum of the studies that will be incorporated. Lastly, applying AI tools in preparing a manuscript can make the process more efficient but, at a risk, cause biasedness when they are not well monitored. Well-conceptualized longitudinal studies and mechanistic investigations should therefore be undertaken in the future to address these shortcomings.

Conclusion

This research seeks to explore the relationship between HPV E6 and ASD, which is a developing topic in the medical field. Although it is still not fully understood how HPV E6 might affect brain development for the disorder, it is known that E6-AP, a protein that HPV E6 targets during infection, has also been associated with the disorder. More work needs to be done to clarify this relationship and to determine whether HPV infection is related to the onset of the disorder in any way. The present review is in response to the above-presented documents and seeks to give a brief overview of the link between HPV E6 and ASD. Therefore, it will be appropriate to mention that the existing connection between these two factors is still subject to debate and additional research is necessary to clarify it. Several aspects of the intricate connection between ASD and HPV E6 protein may be further explored in greater detail. Multiple studies raise the possibility that viral infections increase the risk of neurodevelopmental disorders, but for most potential pathogens, how such associations occur is not known. Researching the molecular mechanism by which E6 disrupts cellular signaling pathways associated with autism may provide a new understanding of both diseases and call for a reconsideration of existing approaches to prevention and treatment. From this literature review, it is seen that there is a network of opportunities where many publishing companies are focusing on interdisciplinary research in which specifically virology, neurobiology, and psychology can be of value in finding new therapeutic approaches to individuals with ASD. Further research is still needed on the relation between HPV and ASD, as well as on the effect of other viral infections on neurodevelopmental outcomes.

Acknowledgment

In writing this article, an AI tool was employed to assist in drafting, language polishing, and organizing the manuscript to maintain accuracy and originality.

Funding:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

None.

Author's Contributions

Abdolvahab Moradi conceptualized the study, supervised the project, reviewed and edited the manuscript, and provided funding acquisition as the corresponding author. Najmeh Sheikhi contributed to the literature search, data analysis, writing the original draft, and figure preparation as a PhD student in Medical Virology. Faezeh Hajizadeh assisted in methodology development, data curation, and manuscript revision as a PhD student in Medical Virology. Jamal Sarvari provided expertise in virology, contributed to the critical review and validation of the content, and offered intellectual input. Zahra Bazi contributed to the biotechnological aspects, including protein interaction analysis and pathway enrichment, and assisted in data interpretation. Iliad Moradi supported the research with laboratory sciences input, including reference management and preliminary data collection as an undergraduate student. All authors read and approved the final manuscript.

References

1. Yeo-Teh NSL, Ito Y, Jha S. High-Risk Human Papillomaviral Oncogenes E6 and E7 Target Key Cellular Pathways to Achieve Oncogenesis. Int J Mol Sci. 2018;19(6):1706.
2. Owais A, Mishra RK, Kiyokawa H. The HECT E3 Ligase E6AP/UBE3A as a Therapeutic Target in Cancer and Neurological Disorders. Cancers (Basel). 2020;12(8):2108.
3. Li S, Hong X, Wei Z, Xie M, Li W, Liu G, et al. Ubiquitination of the HPV Oncoprotein E6 Is Critical for E6/E6AP-Mediated p53 Degradation. Front Microbiol. 2019;10:2483.
4. Martínez-Noël G, Galligan JT, Sowa ME, Arndt V, Overton TM, Harper JW, et al. Identification and proteomic analysis of distinct UBE3A/E6AP protein complexes. Mol Cell Biol. 2012;32(15):3095–106.
5. Drews CM, Brimer N, Vande Pol SB. Multiple regions of E6AP (UBE3A) contribute to interaction with papillomavirus E6 proteins and the activation of ubiquitin ligase activity. PLoS Pathog. 2020;16(1):e1008295.
6. Mortensen F, Schneider D, Barbic T, Sladewska-Marquardt A, Kühnle S, Marx A, et al. Role of ubiquitin and the HPV E6 oncoprotein in E6AP-mediated ubiquitination. Proc Natl Acad Sci U S A. 2015;112(32):9872–7.
7. Ahmad A, Ansari IA. A Comprehensive Review on Cross-talk of Human Papilloma Virus Oncoproteins and Developmental/Self-Renewal Pathways During the Pathogenesis of Uterine Cervical Cancer. Curr Mol Med. 2021;21(5):402–16.
8. Hakanen J. Molecular regulation of forebrain development and neural stem/progenitor cells. 2014.
9. Khatri N, Man HY. The Autism and Angelman Syndrome Protein Ube3A/E6AP: The Gene, E3 Ligase Ubiquitination Targets and Neurobiological Functions. Front Mol Neurosci. 2019;12:109.
10. Mohammadi MR, Ahmadi N, Khaleghi A, Zarafshan H, Mostafavi SA, Kamali K, et al. Prevalence of Autism and its Comorbidities and the Relationship with Maternal

Psychopathology: A National Population-Based Study. Arch Iran Med. 2019;22(10):546–53.
11. Martínez-Noël G, Luck K, Kühnle S, Desbuleux A, Szajner P, Galligan JT, et al. Network Analysis of UBE3A/E6AP-Associated Proteins Provides Connections to Several Distinct Cellular Processes. J Mol Biol. 2018;430(7):1024–50.
12. Kühnle S, Mothes B, Matentzoglu K, Scheffner M. Role of the ubiquitin ligase E6AP/UBE3A in controlling levels of the synaptic protein Arc. Proc Natl Acad Sci U S A. 2013;110(22):8888–93.
13. Roy B, Amemasor E, Hussain S, Castro K. UBE3A: The Role in Autism Spectrum Disorders (ASDs) and a Potential Candidate for Biomarker Studies and Designing Therapeutic Strategies. Diseases. 2023;12(1):7.
14. Ramos-Martínez IE, Ramos-Martínez E, Segura-Velázquez R, Saavedra-Montañez M, Cervantes-Torres JB, Cerbón M, et al. Heparan Sulfate and Sialic Acid in Viral Attachment: Two Sides of the Same Coin? Int J Mol Sci. 2022;23(17):9842.
15. Gentile I, Zappulo E, Militerni R, Pascotto A, Borgia G, Bravaccio C. Etiopathogenesis of autism spectrum disorders: fitting the pieces of the puzzle together. Med Hypotheses. 2013;81(1):26–35.
16. Ganguli S, Chavali PL. Intrauterine Viral Infections: Impact of Inflammation on Fetal Neurodevelopment. Front Neurosci. 2021;15:771557.
17. Wang Z, Fan F, Li Z, Ye F, Wang Q, Gao R, et al. Structural insights into the functional mechanism of the ubiquitin ligase E6AP. Nat Commun. 2024;15(1):3531.
18. Khatri N, Gilbert JP, Huo Y, Sharaflari R, Nee M, Qiao H, et al. The Autism Protein Ube3A/E6AP Remodels Neuronal Dendritic Arborization via Caspase-Dependent Microtubule Destabilization. J Neurosci. 2018;38(2):363–78.
19. Shuid AN, Jayusman PA, Shuid N, Ismail J, Kamal Nor N, Mohamed IN. Association between Viral Infections and Risk of Autistic Disorder: An Overview. Int J Environ Res Public Health. 2021;18(6):2817.
20. Estêvão D, Costa NR, Gil da Costa RM, Medeiros R. Hallmarks of HPV carcinogenesis: The role of E6, E7 and E5 oncoproteins in cellular malignancy. Biochim Biophys Acta Gene Regul Mech. 2019;1862(2):153–62.
21. Enriquez KD, Gupta AR, Hoffman EJ. Signaling Pathways and Sex Differential Processes in Autism Spectrum Disorder. Front Psychiatry. 2021;12:716673.
22. Hall HA, Speyer LG, Murray AL, Auyeung B. Prenatal Maternal Infections and Children's Neurodevelopment in the UK Millennium Cohort Study: A Focus on ASD and ADHD. J Atten Disord. 2022;26(4):616–28.
23. Jones EJ, Gliga T, Bedford R, Charman T, Johnson MH. Developmental pathways to autism: a review of prospective studies of infants at risk. Neurosci Biobehav Rev. 2014;39(100):1–33.
24. Lappé M, Lau L, Dudovitz RN, Nelson BB, Karp EA, Kuo AA. The Diagnostic Odyssey of Autism Spectrum Disorder. Pediatrics. 2018;141(Suppl 4):S272–s9.
25. Bhandari R, Paliwal JK, Kuhad A. Neuropsychopathology of Autism Spectrum Disorder: Complex Interplay of Genetic, Epigenetic, and Environmental Factors. Adv Neurobiol. 2020;24:97–141.
26. Raghavendra P, Pullaiah T. Advances in cell and molecular diagnostics: Academic Press; 2018.
27. Nielsen TC, Nassar N, Shand AW, Jones H, Guastella AJ, Dale RC, et al. Association of Maternal Autoimmune Disease With Attention-Deficit/Hyperactivity Disorder in Children. JAMA Pediatr. 2021;175(3):e205487.
28. Sealey LA, Hughes BW, Sriskanda AN, Guest JR, Gibson AD, Johnson-Williams L, et al. Environmental factors in the development of autism spectrum disorders. Environ Int. 2016;88:288–98.
29. Niyibizi J, Mayrand MH, Audibert F, Monnier P, Brassard P, Laporte L, et al. Association Between Human Papillomavirus Infection Among Pregnant Women and Preterm Birth. JAMA Netw Open. 2021;4(9):e2125308.
30. Kühnle S, Martínez-Noël G, Leclere F, Hayes SD, Harper JW, Howley PM. Angelman syndrome-associated point mutations in the Zn(2+)-binding N-terminal (AZUL) domain of UBE3A ubiquitin ligase inhibit binding to the proteasome. J Biol Chem. 2018;293(47):18387–99.
31. Matentzoglu K, Scheffner M. Ubiquitin ligase E6-AP and its role in human disease. Biochem Soc Trans. 2008;36(Pt 5):797–801.
32. Thatte J, Banks L. Human Papillomavirus 16 (HPV-16), HPV-18, and HPV-31 E6 Override the Normal Phosphoregulation of E6AP Enzymatic Activity. J Virol. 2017;91(22): e01390-17.
33. Kępińska AP, Iyegbe CO, Vernon AC, Yolken R, Murray RM, Pollak TA. Schizophrenia and Influenza at the Centenary of the 1918-1919 Spanish Influenza Pandemic: Mechanisms of Psychosis Risk. Front Psychiatry. 2020;11:72.
34. Di Marco B, Bonaccorso CM, Aloisi E, D'Antoni S, Catania MV. Neuro-Inflammatory Mechanisms in Developmental Disorders Associated with Intellectual Disability and Autism Spectrum Disorder: A Neuro- Immune Perspective. CNS Neurol Disord Drug Targets. 2016;15(4):448–63.
35. Bonfim TA, Giacon-Arruda BCC, Hermes-Uliana C, Galera SAF, Marcheti MA. Family experiences in discovering Autism Spectrum Disorder: implications for family nursing. Rev Bras Enferm. 2020;73(s6):e20190489.
36. Hirota T, King BH. Autism Spectrum Disorder: A Review. Jama. 2023;329(2):157–68.
37. Eigbe IJ, Gamboa CM, Gjini J, Mukherjee J, Dube S. Gut Microbiome and Nutrition Interplay in Regulating and Improving Autism Spectrum Disorder Related Social Symptoms. 2024.

38. Nisticò V, Iacono A, Goeta D, Tedesco R, Giordano B, Faggioli R, et al. Hypermobile spectrum disorders symptoms in patients with functional neurological disorders and autism spectrum disorders: A preliminary study. Front Psychiatry. 2022;13:943098.
39. Patel M, Atluri LM, Gonzalez NA, Sakhamuri N, Athiyaman S, Randhi B, et al. A Systematic Review of Mixed Studies Exploring the Effects of Probiotics on Gut-Microbiome to Modulate Therapy in Children With Autism Spectrum Disorder. Cureus. 2022;14(12):e32313.
40. Wang JCK, Baddock HT, Mafi A, Foe IT, Bratkowski M, Lin TY, et al. Structure of the p53 degradation complex from HPV16. Nat Commun. 2024;15(1):1842.
41. Billingsley CL, Chintala S, Katzenellenbogen RA. Post-Transcriptional Gene Regulation by HPV 16E6 and Its Host Protein Partners. Viruses. 2022;14(7).
42. Shimada M, Yamashita A, Saito M, Ichino M, Kinjo T, Mizuki N, et al. The human papillomavirus E6 protein targets apoptosis-inducing factor (AIF) for degradation. Sci Rep. 2020;10(1):14195.
43. Trajkovski V. Association between Autism Spectrum Disorder and Cancer-a Review from the Literature. Journal of Health and Rehabilitation Sciences. 2024;3(1):21–7.
44. Squarzanti DF, Sorrentino R, Landini MM, Chiesa A, Pinato S, Rocchio F, et al. Human papillomavirus type 16 E6 and E7 oncoproteins interact with the nuclear p53-binding protein 1 in an in vitro reconstructed 3D epithelium: new insights for the virus-induced DNA damage response. Virol J. 2018;15(1):176.
45. Bordonaro M. Hypothesis: Cancer Is a Disease of Evolved Trade-Offs Between Neoplastic Virulence and Transmission. J Cancer. 2018;9(10):1707–24.
46. Chaudhary P, Proulx J, Park IW. Ubiquitin-protein ligase E3A (UBE3A) mediation of viral infection and human diseases. Virus Res. 2023;335:199191.
47. Peng K, Liu R, Jia C, Wang Y, Jeong GH, Zhou L, et al. Regulation of O-Linked N-Acetyl Glucosamine Transferase (OGT) through E6 Stimulation of the Ubiquitin Ligase Activity of E6AP. Int J Mol Sci. 2021;22(19):10286.
48. Buel GR, Chen X, Chari R, O'Neill MJ, Ebelle DL, Jenkins C, et al. Structure of E3 ligase E6AP with a proteasome-binding site provided by substrate receptor hRpn10. Nat Commun. 2020;11(1):1291.
49. Romero-Masters JC, Lambert PF, Munger K. Molecular Mechanisms of MmuPV1 E6 and E7 and Implications for Human Disease. Viruses. 2022;14(10):2138.
50. Meyer U, Feldon J, Yee BK. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. Schizophr Bull. 2009;35(5):959–72.
51. de Bakker T, Journe F, Descamps G, Saussez S, Dragan T, Ghanem G, et al. Restoring p53 Function in Head and Neck Squamous Cell Carcinoma to Improve Treatments. Front Oncol. 2021;11:799993.
52. Nabati F, Moradi M, Mohabatkar H. In silico analyzing the molecular interactions of plant-derived inhibitors against E6AP, p53, and c-Myc binding sites of HPV type 16 E6 oncoprotein. Mol Biol Res Commun. 2020;9(2):71–82.
53. Al-Beltagi M, Saeed NK, Elbeltagi R, Bediwy AS, Aftab SAS, Alhawamdeh R. Viruses and autism: A Bi-mutual cause and effect. World J Virol. 2023;12(3):172–92.
54. Mohammadi Manesh M, Mohebbi A, Yasaghi M, Najafi Memar Z, Javid N, Taziki SA, et al. Low Prevalence of Borna Disease Virus RNA in Patients with Bipolar Major Depression and Schizophrenia in North of Iran. Iran J Virol. 2017;11(2):8-13.
55. Hidayatullah A, Putra WE, Sustiprijatno S, RIFA'I M, Widiastuti D, Heikal MF, et al. Concatenation of molecular docking and dynamics simulation of human papillomavirus type 16 E7 oncoprotein targeted ligands: In quest of cervical cancer's treatment. Anais da Academia Brasileira de Ciências. 2023;95(suppl 1):e20220633.
56. Pintacuda G, Martín JM, Eggan KC. Mind the translational gap: using iPS cell models to bridge from genetic discoveries to perturbed pathways and therapeutic targets. Mol Autism. 2021;12(1):10.
57. Hong D, Iakoucheva LM. Therapeutic strategies for autism: targeting three levels of the central dogma of molecular biology. Transl Psychiatry. 2023;13(1):58.
58. Mehta R, Kuhad A, Bhandari R. Nitric oxide pathway as a plausible therapeutic target in autism spectrum disorders. Expert Opin Ther Targets. 2022;26(7):659–79.