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Research Article

Exposure to Herpes Simplex Virus and Its Interaction with Genetic Polymorphisms of HLA in Autistic Children

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A B S T R A C T

Introduction: Autism spectrum disorders (ASDs) are a group of heterogeneous neurodevelopmental disorders characterised by impaired social interaction and activities, and abnormal repetitive behaviour. As a multifactorial disorder, several environmental, genetic, and immunological factors have been implicated in its pathogenesis.

Aim: To investigate the potential role of Herpes Simplex Virus (HSV) exposure and its interaction with genetic polymorphisms in the Human Leucocyte Antigen (HLA) region in the development of ASD in children

Material and Methods: The study involved 400 autistic children recruited from the National Autism Centre at the Child Welfare Teaching Hospital in Medical City. Blood samples were collected, DNA was extracted, and HLA alleles were genotyped. Enzyme-linked immunosorbent Assay (ELISA) tests were used to detect IgG antibodies for herpes viruses. Statistical analysis included chi-square tests, logistic regression, and correlation analysis. Ethical approval was obtained.

Results: The study revealed that 60.5% of autistic children tested positive for HSV-1, with differences in infection severity across age groups and genders. Genetic analysis revealed specific polymorphisms in the HLA gene, with severe autism cases more frequently associated with mutated heterozygous forms, particularly deletions at novel and new SNPs positions.

Conclusion: There is a link between HSV exposure and specific HLA polymorphisms in autistic children, potentially contributing to ASD pathogenesis. The findings suggest that HLA genotypes may influence immune responses, requiring further research for larger populations.

Keywords: Herpes Simplex Virus, Autism Spectrum Disorder, HLA, Genetic Polymorphisms, Viral Infection

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disability characterised by social and communication impairment and by restricted interest, repetitive and stereotyped behaviours.[1] The Autism and Developmental Disabilities Monitoring Network estimates that autism spectrum disorder affects 1 in 44 children, with a higher prevalence among boys. It often co-occurs with other conditions like epilepsy, depression, anxiety, and Attention Deficit Hyperactivity Disorder (ADHD), characterised by atypical cognitive deficits and executive dysfunction.[2]

Although the main cause of ASD is unknown, it is known to be a multifactorial disorder influenced by genetics and environmental factors, with genetic variation increasing the risk. Early detection is possible, but diagnosis is often delayed. Current research lacks clear neuropathological markers for diagnosis, suggesting that abnormal behaviour is linked to alterations in brain function.[3] Recent studies have explored the role of infectious agents, such as the Herpes Simplex Virus (HSV), in the context of ASD.[4]

HSV is a neurotropic virus that can cause inflammation in the brain, leading to symptoms like seizures, confusion, and cognitive impairments.[5]

The link between HSV and neurodevelopmental disorders, particularly ASD, is being researched. Prenatal or early postnatal exposure to HSV may disrupt normal brain development, increasing the risk of ASD.[6]

The virus's ability to induce inflammation and immune responses in the brain is critical, as it can activate microglia, the brain's resident immune cells, leading to a pro-inflammatory state. Chronic inflammation during critical periods of brain development may contribute to atypical neural circuits observed in individuals with ASD.[7] Understanding HSV's effects on brain development could lead to early diagnosis and intervention strategies.[8]

Additionally, genetic variations, namely in the Human Leucocyte Antigen (HLA) area, have been linked to the vulnerability and presentation of ASD.[9] The HLA system is essential for regulating the immune system and recognising pathogens. It is an important field of study for understanding how immune responses can affect neurodevelopmental outcomes.[10]

HLAs are essential for coordinating immune responses and are natural selection targets for pathogens such as human herpesviruses (HHVs). Genetic variation at multiple HLA loci is strongly associated with modulating immunity to herpes virus infection.[11]

HHVs have been linked to schizophrenia and autism risks, with increased HHV antibodies, higher suicide risk, and structural brain changes. Anti-herpes treatment and anti-inflammatory medications have been shown to improve symptoms.[12]

This study analyses genetic associations across two HHVs and identifies HLA alleles associated with diverse phenotypes.

Methods

Study Design and Setting

A cross-sectional study was conducted at the National Autism Centre, located within the Children's Welfare Hospital, Medical City, Baghdad, between October 2023 and May 2024.

The study included a cohort of 400 children aged 2 to 18 years who were recruited from the aforementioned center. All participants met the diagnostic criteria for autism spectrum disorder (ASD) according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. A comprehensive medical history was obtained for each participant, and detailed demographic data were systematically recorded. Furthermore, standardized neurological and psychological evaluations were performed to confirm the clinical diagnosis of ASD in accordance with DSM-5 criteria. The severity of ASD was assessed using the Childhood Autism Rating Scale. Exclusion criteria comprised children with known genetic syndromes, severe neurological disorders unrelated to ASD, and incomplete medical records.

Sample Collection

Blood samples (5 mL) were collected from all participants. The sample was collected in ethylenediaminetetraacetic acid (EDTA) tubes for DNA extraction and in plain tubes to facilitate serum separation. The samples were maintained at -20 °C until further analysis.

Serological Testing for Herpes Virus Infections (ELISA Testing)

The study focused on detecting antibodies against HSV-1 and HSV-2. Serum samples were tested for IgG antibodies against HSV-1 and HSV-2. Microplates were coated with specific viral antigens, serum samples were added, and secondary antibodies were added for detection. Optical density was measured using an ELISA reader.

DNA Extraction and Genotyping of HLA Polymorphisms

Genomic DNA was extracted from peripheral blood leucocytes using the SimEX Blood DNA extraction kit following the manufacturer's protocol. The concentration and purity of the extracted DNA were assessed using a NanoDrop spectrophotometer. HLA loci were used for high-resolution genotyping, involving PCR-SSO and Luminex technology. DNA samples were amplified, hybridised, and detected using a Luminex 200 system. HLA alleles were

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assigned based on hybridisation signals. In general, PCR has been applied across several medical areas.[13–24]

Statistical Analysis

The study utilised Statistical Package for the Social Sciences (SPSS) version 26, analysing data . Statistical tests identified significant differences between study groups, and logistic regression assessed the association between HLA alleles and herpes virus seropositivity in autistic children.

Ethical Considerations

This study was approved by the Ethical Committee of the College of Medicine, University of Al-Iraqia, Baghdad, Iraq. Written informed consent was obtained from the parents or legal guardians, and assent from all participating children was obtained prior to sample collection.

Results

Results of Serological Testing

Immunoglobulin assays were performed on samples to detect HSV-1 and HSV-2. The mean concentration of IgG for HSV-1 was 21.58266 ± 16.961378 (IU/mL), whereas for HSV-2, it was 8.68502 ± 5.717347 (IU/mL) (Figure 1). Based on the cut-off value (0.43), the majority of patients tested for HSV-1 had a positive result (60.5%), whereas around 74.5% of patients screened for HSV-2 had a negative result (Figure 2).

Significant differences were observed only among patients' age groups for herpes virus type 1 (HSV-1). Specifically, a higher percentage of patients in the 3-6-year age group exhibited mild, moderate, and severe forms of the infection (66.1%, 77.9%, and 41.9%, respectively) than patients in other age groups. This difference was statistically significant (Likelihood ratio: 19.566, df: 8, p = 0.012). Similarly, in the case of the herpes virus-2 infection, the three types of ASD disease were mainly detected in children aged 3−6 years. However, these differences were not statistically significant (p > 0.05), as shown in Table 1.

When it comes to the relationship between patients' gender and the severity of ASD in relation to herpes infection type 1, it was found that male patients had significantly higher rates of moderate and severe infections (75.2% and 71.0%, respectively) compared to female patients. On the other hand, mild infections were more common among female patients (51.8%). These findings were statistically significant (1^2: 12.613, df: 2, p = 0.002). However, no notable differences were detected in patients' gender or the severity of their ASD in relation to herpes infection type 2 (p > 0.05) (Table 2).

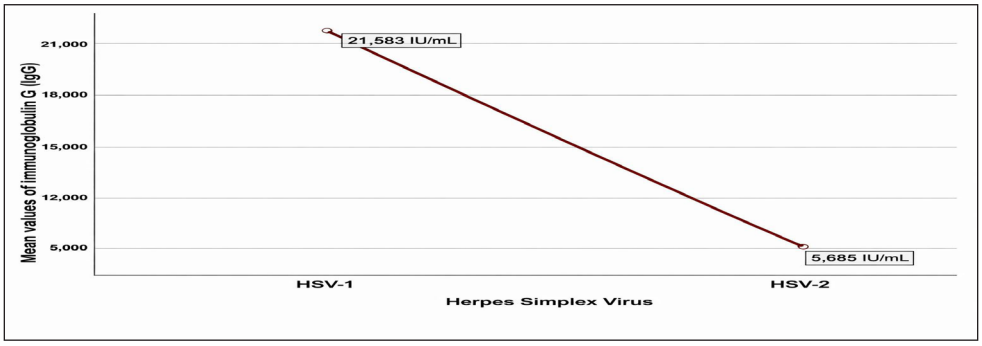

Figure 1.Mean Values of IgG Concentration for HSV-1 and HSV-2 (Each N = 200)

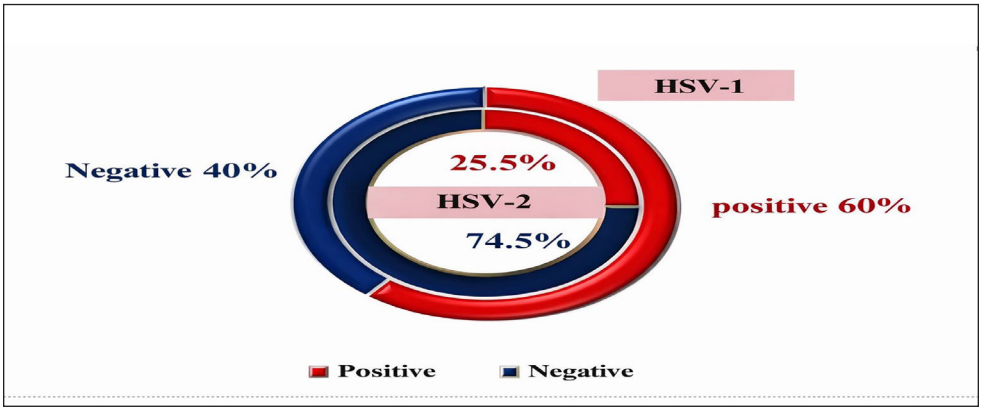

Figure 2.HSV Positivity among the Study Sample (Each N = 200)

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Table 1.Distribution of Patients by Severity of ASD Disease and Age Groups among Herpes Virus Groups

(N = 400)

Patients' Age- Group (Years)	HSV-1[a]						HSV-2[b]					
	ASD Severity						ASD Severity					
	Mild (56)		Moderate (113)		Severe (31)		Mild (47)		Moderate (131)		Severe (22)	
	n	%	n	%	n	%	n	%	n	%	n	%
< 3	2	3.6	2	1.8	-	-	1	2.1	-	-	-	-
3–6	37	66.1	88	77.9	13	41.9	35	74.5	92	70.2	15	68.2
7–10	13	23.2	17	15.0	10	32.3	7	14.9	35	26.7	5	22.7
11–13	3	5.4	5	4.4	6	19.4	4	8.5	4	3.1	2	9.1
≥ 14	1	1.8	1	0.9	2	6.5	-	-	-	-	-	-

a: Likelihood Ratio: 19.566, df: 8, p = 0.012, b: Likelihood Ratio: 7.975, df: 6, p = 0.240 ASD: Autism Spectrum Disorder; HSV-1: Herpes Simplex Virus type 1; HSV-2: Herpes Simplex Virus type 2; df: degrees of freedom; p: probability value (p-value).

Table 2.Distribution of Patients by Severity of ASD Disease and Gender among Herpes Virus Groups

(N = 400)

Patients' Gender	HSV-1[a]						HSV-2[b]					
	ASD Severity						ASD Severity					
	Mild (56)		Moderate (113)		Severe (31)		Mild (47)		Moderate (131)		Severe (22)	
	n	%	n	%	n	%	n	%	n	%	n	%
Female	29	51.8	28	24.8	9	29.0	18	38.3	49	37.4	9	40.9
Male	27	48.2	85	75.2	22	71.0	29	61.7	82	62.6	13	59.1

a: : 12.613, df: 2, p = 0.002, b: : 0.101, df: 2, p = 0.951 ASD: Autism Spectrum Disorder; HSV-1: Herpes Simplex Virus type 1; HSV-2: Herpes Simplex Virus type 2; df: degrees of freedom; χ^2: chi-square test; p: probability value (p-value).

Significant differences in maternal age were found among participants with varying severity of ASD in the herpes virus infection-1 group. The mean maternal age was significantly higher in cases of severe disease (36.84 ± 3.796 years) than in moderate and mild disease (31.51 ± 4.283 and 30.63 ± 5.922 years, respectively). This difference was statistically significant (F = 2.513, df: (26, 173), p = 0.000). In contrast, there was no notable difference in the age of the mothers of participants and the severity of ASD between the herpes virus infection-2 group and the control group (p > 0.05) (Table 3).

Furthermore, there were significant differences in the ages of participants' fathers in relation to the severity of ASD disease forms in the HSV-1 infection group. Specifically, the mean age of fathers with severe forms of the disease was significantly higher than that of those with moderate forms, which in turn was higher than that of those with mild forms (40.26 ± 5.151 vs 34.22 ± 4.561 vs 33.95 ± 6.013, respectively) (F = 2.294, df: (26, 173), p = 0.001). However, no significant association was found between the ages of fathers of participants and the severity forms of ASD disease in relation to herpes virus infection type-2 (p > 0.05) (Table 4).

There were significant differences in the severity of ASD between patients with a positive family history of ASD and those with a negative family history. Among patients with a positive family history, a higher proportion had mild, moderate, and severe forms of ASD (60.7%, 86.7%, and 83.9%, respectively) than those with a negative family history (39.3%, 13.3%, and 16.1%, respectively). This difference was statistically significant (x^2 x^2: 15.795, df: 2, p = 0.000). However, there was no significant association between the family history and severity of ASD in the herpes virus infection-2 group (p > 0.05) (Table 5).

Likewise, a significant association was identified between the history of comorbidities and severity of ASD in the HSV-1 group, as the proportion of moderate form of ASD was significantly higher among patients with a positive history of comorbidities, mainly ADHD, than those with a negative history (80.5% vs 16.8%, respectively). In contrast, the proportions of mild and severe forms of ASD were

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significantly lower among patients with a positive history of comorbidities than those with a negative history (26.8% vs 71.4% and 12.9% vs 51.6%, respectively). Nevertheless, no significant association was found between comorbidity history and the severity of ASD in the HSV-2 group (Table 6).

Table 3.Association of Mean Maternal Age with ASD Disease Severity among Herpes Simplex Virus Groups

ASD Severity	Herpes Simplex Virus Groups					
	HSV-1[a] (N = 200)			HSV-2[b] (N = 200)		
	n	Mean ± SD (Years)	Mean difference[c]	n	Mean ± SD (Years)	Mean difference[c]
Mild	56	30.63 ± 5.922	-	47	30.87 ± 4.416	-
Moderate	113	31.51 ± 4.283	0.88	131	31.16 ± 4.015	0.29
Severe	31	36.84 ± 3.796	6.21	22	30.64 ± 3.749	-0.23

a: F = 2.513, df: (26, 173), p = 0.000, b: F = 1.197, df: (19, 180), p = 0.264, c: Mean difference from the Mild disease group ASD: Autism Spectrum Disorder; HSV-1: Herpes Simplex Virus type 1; HSV-2: Herpes Simplex Virus type 2; SD: Standard Deviation; N: total number of participants; n: number of cases; df: degrees of freedom; F: Analysis of Variance (ANOVA) test statistic; p: probability value (p-value).

Table 4.Association of Mean Age of Fathers of Participants with ASD Disease Severity among Herpes Simplex Virus Groups

ASD Severity	Herpes Simplex Virus Groups					
	HSV-1[a] (N = 200)			HSV-2[b] (N = 200)		
	n	Mean ± SD (Years)	Mean difference[c]	n	Mean ± SD (Years)	Mean difference[c]
Mild	56	33.95 ± 6.013	-	47	34.06 ± 5.475	-
Moderate	113	34.22 ± 4.561	0.27	131	34.26 ± 4.355	0.2
Severe	31	40.26 ± 5.151	6.31	22	32.86 ± 2.713	-1.2

a: F = 2.294, df: (26, 173), p = 0.001, b: F = 1.206, df: (24, 175), p = 0.243, c: Mean difference from the Mild disease group
ASD: Autism Spectrum Disorder; HSV-1: Herpes Simplex Virus type 1; HSV-2: Herpes Simplex Virus type 2; SD: Standard Deviation; N: total number of participants; n: number of cases; df: degrees of freedom; F: Analysis of Variance (ANOVA) test statistic; p: probability value (p-value).

Table 5.Distribution of Patients by Severity of ASD Disease and Family History of ASD among Herpes Virus Groups

(N = 400)

Family History of ASD	HSV-1[a]						HSV-2[b]					
	ASD Severity						ASD Severity					
	Mild (56)		Moderate (113)		Severe (31)		Mild (47)		Moderate (131)		Severe (22)	
	n	%	n	%	n	%	n	%	n	%	n	%
No	22	39.3	15	13.3	5	16.1	9	19.1	37	28.2	6	27.3
Yes	34	60.7	98	86.7	26	83.9	38	80.9	94	71.8	16	72.7

a: $x^2 x^2$: 15.795, df: 2, p = 0.000., b: $x^2 x^2$: 1.508, df: 2, p = 0.470 ASD: Autism Spectrum Disorder; HSV-1: Herpes Simplex Virus type 1; HSV-2: Herpes Simplex Virus type 2; df: degrees of freedom; χ^2: chi-square test statistic; p: probability value (p-value); n: number of cases; %: percentage.

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Table 6.Distribution of Patients by Severity of ASD Disease and Presence of Comorbidities among Herpes Virus Groups

(N = 400)

Presence of Comorbidities	HSV-1[a]						HSV-2[b]					
	ASD Severity						ASD Severity					
	Mild (56)		Moderate (113)		Severe (31)		Mild (47)		Moderate (131)		Severe (22)	
	n	%	n	%	n	%	n	%	n	%	n	%
None	40	71.4	19	16.8	16	51.6	23	48.9	62	47.3	12	54.5
ADHD	15	26.8	91	80.5	4	12.9	21	44.7	57	43.5	9	40.9
Epilepsy	-	-	1	0.9	11	35.5	2	4.3	6	4.6	-	-
Brain atrophy	1	1.8	-	-	-	-	-	-	2	1.5	1	4.5
Epilepsy and brain tumour	-	-	1	0.9	-	-	-	-	-	-	-	-
Down syndrome	-	-	-	-	-	-	-	-	2	1.5	-	-
Epilepsy and ADHD	-	-	-	-	-	-	1	2.1	1	0.8	-	-
Tourette syndrome	-	-	1	0.9	-	-	-	-	1	0.8	-	-

a: Likelihood Ratio: 107.608, df: 10, p = 0.000, b: Likelihood Ratio: 7.918, df: 12, p = 0.792

ASD: Autism Spectrum Disorder; HSV-1: Herpes Simplex Virus type 1; HSV-2: Herpes Simplex Virus type 2; DM: Diabetes Mellitus; df: degrees of freedom; n: number of cases; %: percentage; Likelihood Ratio: likelihood ratio test statistic; p: probability value (p-value).

Results of Genetic Polymorphism

A total of 21 patients, equally distributed among mild, moderate, and severe autism subgroups, were purposively selected rather than randomly sampled to ensure adequate representation of autism severity levels for the investigation of genetic polymorphisms. Six single nucleotide polymorphisms (SNPs) of one selected gene (HLA) were investigated; One variant had not been previously reported and was therefore considered a novel single nucleotide polymorphism (novel SNPs). Additionally, two other variants were also identified as novel (New 29943645–29943646 and New 29943691–29943692). Other identified variants included rs2735112, rs140855847, and rs1436548546.

When comparing the genetic variation (mutation) in autism severity, we found that only three specific variants in the HLA gene, namely a novel variant, New 29943691−29943692, and rs140855847, showed significant differences in genetic variations in severe cases of autism and the comparative subgroups of disease severity. The majority of severe autism cases had a genetic alteration in the form of a mutated heterozygous or mutated heterozygous with deletion of the novel SNPs position in the HLA gene, compared to those with mild forms of the disease who had a wild homozygous genetic makeup (100% or 100% vs 43.8%, respectively) (Fisher's Exact Test: 9.953, p = 0.003) (Table 7 and Figure 3).

Most severe cases of autism are associated with a genetic variation involving a heterozygous mutation in the HLA gene, specifically a deletion of the SNPs New 29943691−29943692. This variation was detected in 71.4% of severe cases compared with 50% of mild and moderate cases. Statistical analysis using Fisher's exact test yielded a test statistic of 7.689 with a p-value of 0.025. These findings are presented in Table 7 and Figure 4.

In addition, it was discovered that there are genetic differences in additional SNPs of the HLA gene, namely at positions 29943645−29943646 and rs2735112. These variations include both overall mutant heterozygous with deletion and mutated heterozygous with insertion, with a prevalence of 100% across all three types of autism severity.

However, SNP of the HLA gene, specifically rs1436548546, did not exhibit any notable variations in relation to the severity of autistic disorder (p > 0.05) (Table 7 and Figure 5).

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Table 7.Distribution of Autistic Children by Severity and Genetic Variation of the HLA Gene (New SNP (Novel SNP), SNP New 29943691–29943692, and SNP rs1436548546)

(N = 21)

Variation of the HLA Gene (Novel SNP)	Autism Spectrum Disorder						Total
	Mild (7)		Moderate (7)		Severe (7)		
	n	%	n	%	n	%	
Wild homozygous	7	43.8	7	43.8	2	12.5	16
Mutated heterozygous	-	-	-	-	3	100.0	3
Mutated heterozygous with deletion	-	-	-	-	2	100.0	2

ASD: Autism Spectrum Disorder; HLA: Human Leukocyte Antigen; SNP: Single Nucleotide Polymorphism; n: number of cases; %: percentage; Fisher Exact Test: Fisher's exact test statistic; p: probability value (p-value).

Variation of HLA gene (SNP New 29943691– 29943692)	Autism Spectrum Disorder						Total
	Mild (7)		Moderate (7)		Severe (7)		
	n	%	n	%	n	%	
Wild homozygous	7	50.0	5	35.7	2	14.3	14
Mutated heterozygous with deletion	-	-	2	28.6	5	71.4	7

Variation of HLA gene (SNP rs1436548546)	Autism Spectrum Disorder						Total
	Mild (7)		Moderate (7)		Severe (7)		
	n	%	n	%	n	%	
Wild homozygous	6	37.5	6	37.5	4	25.0	16
Mutated heterozygous	1	20.0	1	20.0	3	60.0	5

Fisher's Exact Test: 1.892, p = 0.545

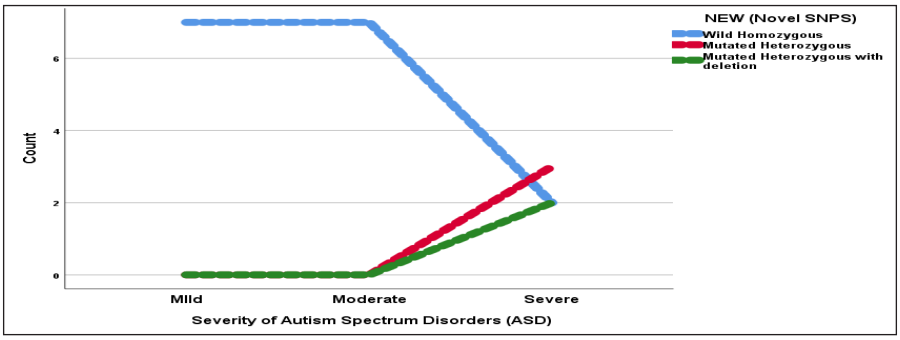
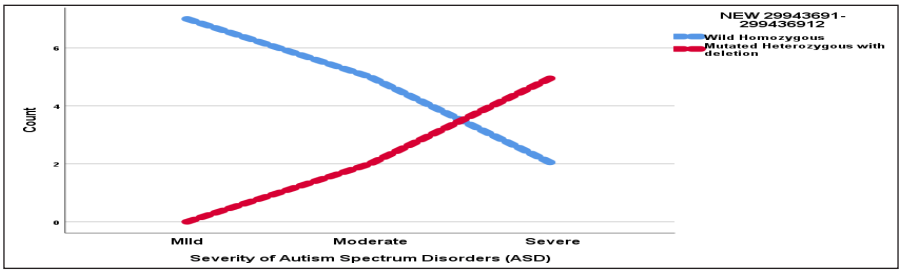


Figure 3.Distribution of Autistic Children by Disease Severity and Genetic Variation of HLA Gene New SNPs (Novel SNPs) (N = 21)



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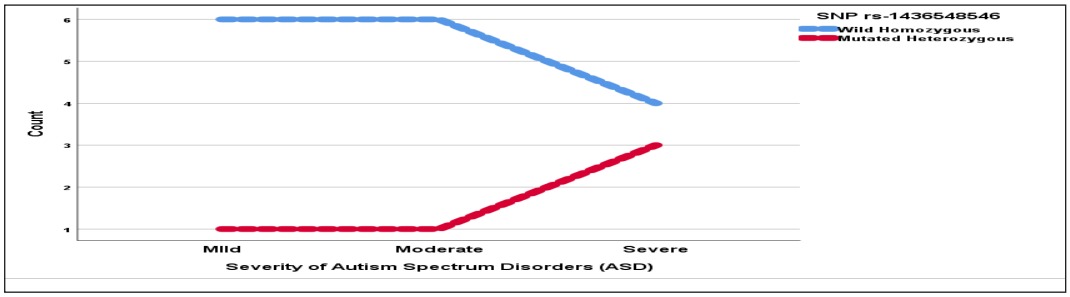

Figure 5.Distribution of Autistic Children by Disease Severity and Genetic Variation of HLA Gene (SNP rs1436548546) (N = 21)

Discussion

Researchers suggest that a viral trigger may be involved in ASD development, requiring study of Herpesviridae family viruses, which target the central nervous system and interact with the host immune system, potentially initiating additional immunological illnesses.[25]

The study reveals elevated IgG antibodies against HSV-1, suggesting long-lasting infection or extensive transmission. Lower levels of IgG for HSV-2 are consistent with previous research[25] . Age disparities exist, with children aged 3–6 years being more susceptible to severe symptoms. Gender differences may be biological or societal. No significant correlation was found between age groups and ASD severity in HSV-2 infection.

This study enrolled only patients with autism, unlike a previous study by Gentile et al. and Mora et al., which found a higher prevalence of anti-HSV IgG antibodies in children with ASD than in healthy controls.[25,26]

The study reveals a strong link between family history of ASD and severe ASD in HSV-1-infected patients, suggesting that genetic factors may significantly influence ASD severity. However, for HSV-2-infected patients, the severity of ASD was not significantly influenced by family history, which suggested that other factors may play a role. This highlights the potential impact of familial genetic factors on ASD severity, as previously reported in studies in the USA and Sweden.[27]

The average age of mothers in this study was early thirties, with most having children in their mid-twenties. This suggests that women had children earlier but delayed further childbirth or had fewer children later.[28] It has been observed that older paternal age increases the risk of certain disorders, such as autism and ADHD.[29]

The research highlights a unique pattern where both maternal and paternal ages are critical factors in determining the severity of ASD among children infected with herpes virus-1, a trend not observed in herpes virus-2 infections.[30]

The study found a significant link between HSV-1 and ASD, especially in severe cases with ADHD and epilepsy, while HSV-2 did not show any such association. The high prevalence of ADHD in both herpes virus groups suggests a possible link. ADHD and ASD are neurodevelopmental disorders that often co-occur, possibly due to shared genetic, environmental, and neurobiological factors.[31]

Viral infections during pregnancy may increase the risk of psychopathology and may lead to elevations in cytokine levels and stimulation of vagus nerves, which in turn, stimulate the CNS to increase cytokine levels and activate microglia.[32]

Cytokines may interact with Major Histocompatibility Complex (MHC) to affect learning and memory, and may interact with genetic polymorphisms. Despite limitations, viral agents may play a role in motor hyperactivity in children and adolescents with ADHD.[33]

HSV-2 has a less significant association with conditions like epilepsy, brain atrophy, Down syndrome, and Tourette syndrome, possibly due to its unique pathophysiological profile. Despite its impact in certain areas, HSV-2 does not significantly impact these conditions compared to HSV-1, which has a stronger link with severe neurological outcomes.

The exact cause of ASD is still unclear, but it is believed to be influenced by both hereditary and environmental factors.[34]

Recent genetics and environmental research indicate that immune-related genes and responses to environmental stimuli significantly contribute to the development of ASD.[35]

Previous research has revealed multiple genetic markers and locations within the HLA gene that are linked to autism, highlighting the intricate genetic foundation of the disorder.[36]

The study identifies novel SNPs, advancing current knowledge by uncovering previously unexplored genetic variations, providing more depth to investigations on the genetic factors underlying autism.[37]

The study identifies a novel SNP linked to autism severity, with severe cases showing mutated variants, while milder cases displayed wild-type homozygous variants. Other SNPs, like rs1408f55847 and New 29943691–29943692, showed

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significant genetic variations between severe and milder autism cases. These new variants could reveal unexplored disease progression mechanisms.

The HLA gene's specific genetic markers could predict the progression and severity of autism, highlighting the complexity of the genetic basis of the condition and its role in immune system regulation.[38–40]

Conclusion

The study indicates a link between HSV exposure and specific HLA polymorphisms in autistic children, potentially influencing ASD pathogenesis, requiring further research for validation and therapeutic strategies.

Authors' Contribution: All authors contributed equally to the study design, data collection, laboratory analysis, statistical analysis, interpretation of results, and manuscript preparation. All authors reviewed and approved the final version of the manuscript.

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