The Egyptian Journal of Hospital Medicine (October 2025) Vol. 101, Page 4787-4795

Study of SCN1A and SCN2A Polymorphism in Children with Autistic Spectrum Disorders

Zeinab Sabri Abouzouna[*1], Sameh Abdalla Abd-Elnabi[1], Mohamed Shokry Elharoun[1], Mahmoud Ibrahem Saad Ibrahem[1], Noran Talaat Aboelkhair[2], Heba Badawy Abd Elsalam[1]

Departments of [1]Pediatric and [2]Clinical Pathology, Faculty of Medicine, Menoufia University, Menoufia, Egypt

***Corresponding Author:** Zeinab Sabri Abouzouna, **Mobile:** (+20) 01002398916, **E-mail:** zeinab_sabri@yahoo.com

ABSTRACT

Background: Autism spectrum disorder (ASD) is a set of neurobehavioral diseases. Most excitable cells depend on voltage-gated sodium channels to function normally. The alpha 1 and 2 subunits of the sodium channel are coded by the SCN1A and SCN2A genes.

Objective: To investigate the role of SCN1A and SCN2A gene polymorphisms in children with ASD.

Patients and Methods: This case-control study was conducted on one hundred children divided as follows: 50 children with autism and 50 healthy controls. The *rs 2162600 T/C* of *SCN1A* gene and *rs 2304016 A/G* of *SCN2A* gene polymorphisms were genotyped via TaqMan allelic discrimination polymerase chain reaction.

Results: It was found that as the age of the mother increases, the risk of autism increases and that first-born children have a greater risk for ASD compared to the later-born ones. The prevalence of epilepsy, obesity, and gestational hypertension in the family history was significantly higher in patients with autism. The frequency of CC and CT genotypes of *SCN1A rs 2162600* was higher in the autistic group in comparison with controls. However, this did not reach statistical significance. In addition, no significant difference was observed concerning *SCN2A rs 2304016* genotype and allele distribution between the studied groups.

Conclusions: No significant association was noticed between *SCN1A rs 2162600* and *SCN2A rs 2304016* genotypes and alleles with ASD in children.

Keywords: Autistic spectrum disorders, Gene polymorphism, *SCN1A*, *SCN2A*, Voltage-gated sodium channels.

INTRODUCTION

Autism is a neurodevelopmental condition characterized by delayed social, communicative, and behavioral development. Autism spectrum disorder (ASD), a broad category of developmental diseases affecting both children and adults, include autism as a prevalent developmental disorder. Autism usually manifests and is diagnosed 36 months of age [(1)].

Three to six children out of every 1000 are thought to be affected by ASD, with boys more likely to have this condition than females. Epilepsy and several hereditary diseases are linked to ASD, and mental retardation is linked to autism [(2)]. Numerous prenatal aspects, including older parental generations and maternal diabetes during pregnancy, are associated with an increased risk of autism [(3)].

Multiple explanations of autism have been suggested. However, the idea of autism and other autistic spectrum diseases' causation is still not fully understood [(4)]. It was formerly believed that genetics account for around 90% of a child's risk of having autism. However, environmental issues have been underestimated, and inheritances overestimated, for their contributions to ASD [(5)].

Autism often begins during infancy or childhood and progresses steadily without remission, with symptoms appearing progressively from the age of 6 months. Then, it becomes established by the age of two or three years and continues throughout adulthood [(6)]. Children with autism often act strangely, flapping their hands, repeating certain words, throwing tantrums, and playing with just one item, among other atypical behaviors [(7)].

Autism may be caused by several linked gene loci, according to clinical genetic investigations and mathematical models. Moreover, environmental and epigenetic variables may be involved [(8)].

Voltage-gated sodium ion channels (VGSCs) are heteromeric proteins that help brain neuronal cells generate and transmit action potential. They are membrane-associated proteins that move sodium ion currents through a gradient of concentration into cell [(9)].

These channels are composed of two subunits: a primary one (encoded by the genes SCN1A-SCN11A) and a secondary one (encoded by the genes SCN1B-SCN4B) [(10)]. Various antiepileptic medications target the α subunit, creating the sodium channel pore. The α and β subunits interact to modify the channel characteristics and alpha subunit location [(11)].

The SCN1A and SCN2A genes encode for the sodium channel alpha 1 and alpha 2 subunits, respectively. They are found at position 2q24.3 on chromosome 2 [(12)]. A highly conserved gene family of sodium channel-subunit genes is composed of them. Given that the action potential initiation and spread are critically impacted by SCN1A and SCN2A, mutations of these genes cause a considerable burden of neurological disease [(13)].

In the human genome, sodium channel genes are among the most highly conserved genes, and they share numerous sequence similarities with sodium channels found in invertebrates and prokaryotes. Major clinical consequences of deviations from normal channel function include seizures, intellectual impairment, behavioral abnormalities, and difficulties with

Received: 25/04/2025
Accepted: 26/06/2025

movement. SCN1A, SCN2A, and SCN8A genes together account for more than 95% of brain sodium channel transcripts, which also result in most of the known sodium channelopathies in the brain [14].

Thus, the current study aims to investigate the role of *SCN1A* and *SCN2A* gene polymorphism in children with ASD.

PATIENTS AND METHODS

Patients:

This case-control study was conducted on 100 children from the Neurology Clinics of the Pediatric Department at Faculty of Medicine, Menoufia University, during April 2021 and May 2024. The children under study were classified into 2 groups as follows; The patient group (autistic group) included 50 children with autism diagnosed with idiopathic autism based on the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) criteria and according to the Childhood Autism Rating Scale (CARS). The patients' group included 38 males and 12 females, with ages ranging between 3 and 8 years. The control group included 50 healthy age- and gender-matched children.

Exclusion criteria were children with organic brain lesions, autoimmune diseases (e.g., autoimmune encephalopathy), and abnormal movements such as chorea and athetosis.

Methods:

All participants were subjected to the following:

1- Detailed History Taking and Clinical Examination:

Personal history included name, age, sex, residence, and birth order. The history of illness in the patients' group included the onset, course, and duration of illness as well as medications given. History also included perinatal history as prenatal history: prenatal complications (maternal illness) such as diabetes, hypertension, and infection. Natal history included the duration of pregnancy, mode of delivery, and birth weight. Postnatal history comprised respiratory difficulty, jaundice, and convulsions. Developmental history included motor development as timing of head support, sitting, crawling, and walking. Mental development included social development in infancy (social smile, knowing mother, reaction to strangers, and eye contact), speech development in early childhood, and school achievement and learning ability in late childhood. Nutritional history included types of feeding in infancy. Family history included family history of similar conditions, age of parents, health condition, occupation, education, socioeconomic level, and consanguinity. Full clinical examination involved general examinations such as heart rate, respiratory rate, blood pressure, and anthropometric measurements (weight, height, and BMI on Z-score). The systemic examination involved neurological, chest, cardiac, and abdomen examinations.

2- Laboratory Investigations:

Estimation of serum calcium level and liver function tests (AST and ALT) were done on Au 680 autoanalyzer utilizing kits supplied by Beckman (Beckman, USA). Detection of gene polymorphism of *SCN1A* gene *rs 2162600 T /C* and *SCN2A rs 2304016 A/G* was conducted by allelic discrimination PCR. The DNA was isolated from EDTA blood samples using a DNA extraction Kit (Thermofisher Scientific, USA) according to the manufacturer's protocol. The extracted DNA was stored at −80 °C till genotyping. The genotyping was performed via real-time PCR using the ABI TaqMan allelic discrimination kit provided by Applied Biosystems, USA.

The sequences utilized for the probes were: (VIC for T allele/ FAM for C allele) ACATTTTCCCTGGTGACATTTCCAC(**T/C**)GTTT GACCATTTAGCTGTGTCAAGA for *rs 2162600* and (VIC for A allele/ FAM for G allele) GGCTGAAGTGTTTTACAGGATTTTA(**A/G**)TGAT TCTTTCTATTCCTTT CTCTTT for *rs 2304016*. The PCR reaction worked in a total volume of 20 µl including 10 µl TaqMan genotyping master mix, 1.25 µl custom TaqMan assay (primer/probe) 40×, 5 µl genomic DNA, and 3.75 µl nuclease-free water. The conditions for cycling were as follows: initial denaturation at 94 °C for 15 min, followed by 50 cycles of denaturation at 94 °C for 15 sec and annealing at 62 °C for 30 sec. Then, 96-well plates were loaded in the 7500 Real-Time PCR System (Applied Biosystems, USA). The allelic discrimination plot for *SCN1A* gene (*rs2162600*) is shown in (**Fig. 1).**

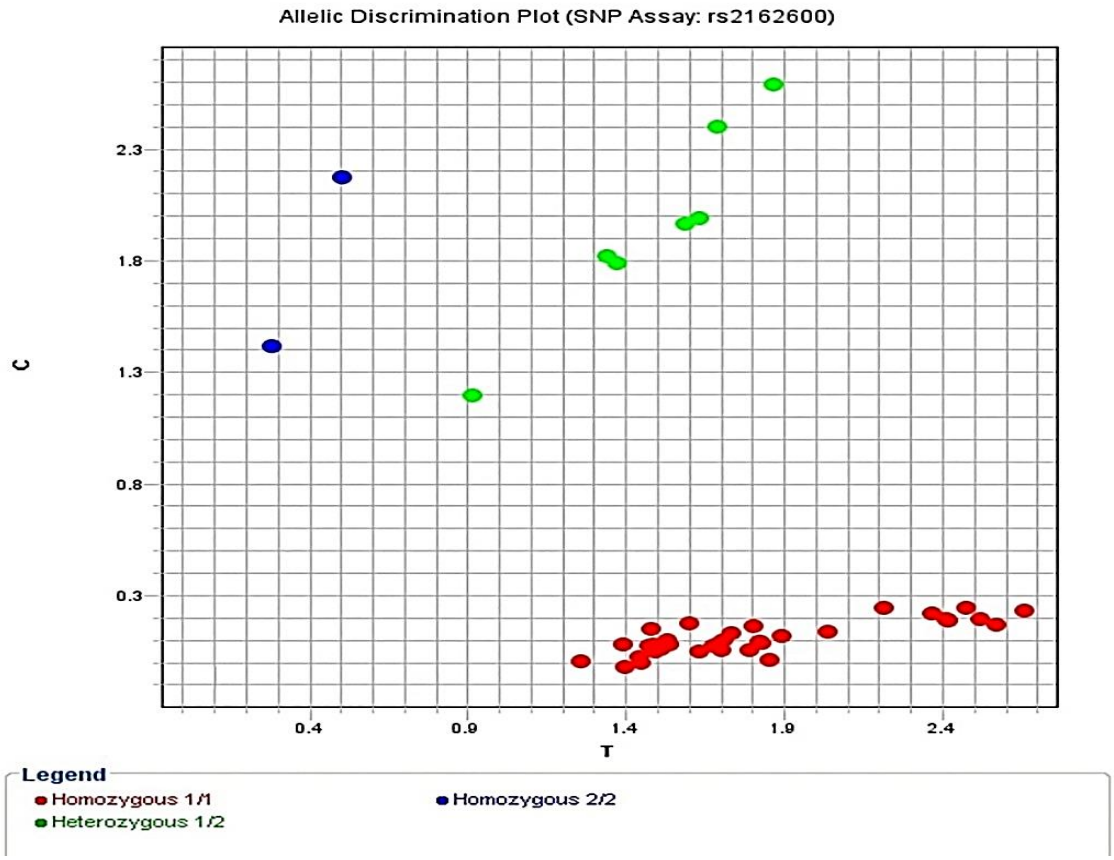

Figure (1): The allelic discrimination plot for *SCN1A* gene (*rs2162600*).

Ethical approval:

Approval was granted by the Menoufia Faculty of Medicine Ethics Committee (Approval number: 3/2021PEDI 149), and informed consent was obtained from the patients' guardians. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

Data collection and organization were don. While, statistical analysis was conducted using SPSS version 22.0 on an IBM personal computer. Quantitative data was shown using the mean ± standard deviation (SD), and range. Numbers and percentages were used to display the qualitative findings. Among the analytical statistics employed were the χ^2-test, the t-test for parametric data, and the Mann-Whitney test for non-parametric data. The univariate and multivariate regression analysis were used to define odds ratio (OR), while95% confidence interval (CI) was used to define significance of the risk. Also, the p-value was deemed significant at $p < 0.05$ for χ^2-test, t-test, and Mann-Whitney test.

RESULTS

A significant difference was observed between the autistic group and controls regarding the 2nd and 3rd birth order, maternal age, family history for comorbidities, gestational hypertension, and delayed crying. Mothers of autistic children were older than mothers of controls (p=0.001). Furthermore, 16% of the autistic group had a positive family history of ADHD, 12% had a positive family history of epilepsy, and 8% had a positive family history of obesity while all controls had no family history of comorbidities (p<0.001). In addition, gestational hypertension and delayed crying were significantly higher in the autistic group (p=0.047 and p<0.001, respectively) **(Table 1)**.

However, no significant difference was noted between the autistic group and controls regarding residence, consanguinity, socioeconomic level, paternal education, and occupation (p>0.05). Moreover, there was no significant difference regarding mode of delivery, duration of pregnancy, and birth weight **(Table 1)**.

Table (1): Socio-demographic data and perinatal data of the studied groups.

Studied variable		Autistic group (N=50)	Control group (N=50)	Test of significance	P value
Age (years):					
Mean ±SD		4.88±1.43	5.43±1.94	**U**	0.429
Median		4.60	5.00	0.792	
Range		3.00 – 8.00	3.00 – 10.0		
Sex:		**N (%)**	**N (%)**	χ^2	
Male		38(76.0)	42(84.0)		
Female		12(24.0)	8(16.0)	1.00	0.317
Residence:	Rural	32(64.0)	26(52.0)	χ^2	
	Urban	18(36.0)	24(48.0)	1.47	0.224
Consanguinity:	Positive	10(20.0)	14(28.0)	χ^2	
	Negative	40(80.0)	36(72.0)	0.877	0.439
Order of birth:				χ^2	
1st		22(44.0)	16(32.0)	1.52	0.216
2nd		12(24.0)	28(56.0)	10.6	**0.001***
3rd		16(32.0)	6(12.0)	5.84	**0.015***
Socioeconomic level:				χ^2	
Low		16(32.0)	12(24.0)	0.79	0.372
Moderate		20(40.0)	16(32.0)	0.69	0.404
High		14(28.0)	22(44.0)	2.77	0.095
Paternal education:				χ^2	
Low		12(24.0)	8(16.0)	1.00	0.317
Middle		28(56.0)	24(48.0)	0.64	0.423
High		10(20.0)	18(36.0)	3.17	0.074
Paternal occupation:	Yes	40(80.0)	44(88.0)	χ^2	
	No	10(20.0)	6(12.0)	1.19	0.275
Maternal age / years:				**U**	
Mean ±SD		29.7±4.42	22.8±2.75	5.35	**0.001***
Median		28.0	23.0		
Range		24.0 – 38.0	18.0 – 27.0		
Mode of delivery:		No (%)	No (%)	χ^2	
Vaginal		14(28.0)	12(24.0)		
Cesarean		36(72.0)	38(76.0)	0.208	0.648
Prenatal complications:				χ^2	
No		34(68.0)	46(92.0)	9.00	**0.002***
Diabetes mellitus		6(12.0)	4(8.00)	0.44	0.509
Gestational hypertension		6(12.0)	0(0.00)	3.94	**0.047***
Hemorrhage		2(4.00)	0(0.00)	0.34	0.557
Infection		2(4.00)	0(0.00)	0.34	0.557
Duration of pregnancy:		**N (%)**	**N (%)**	χ^2	
Preterm		16(32.0)	15(30.0)		
Full term		34(68.0)	35(70.0)	0.0	0.648
Birth weight:	Normal	32(64.0)	36(72.0)	χ^2	
	Low birth weight	18(36.0)	14(28.0)	0.735	0.391
Postnatal complications:				χ^2	
No		22(44.0)	36(72.0)	8.04	**0.004***
Delayed crying		14(28.0)	0(0.00)	13.2	**<0.001***
Preterm labor		6(12.0)	6(12.0)	0.00	1.00
Jaundice		6(12.0)	8(16.0)	0.42	0.512
RDS		2(4.00)	0(0.00)	0.34	0.557
Type of feeding:				χ^2	
Breastfeeding		30(60.0)	40(80.0)		
Artificial feeding		20(40.0)	10(20.0)	4.76	**0.029***
Family history:				χ^2	
No		32(64.0)	50(100)	18.7	**<0.001***
ADHD		8(16.0)	0(0.00)	5.98	**0.014***
Epilepsy		6(12.0)	0(0.00)	3.84	0.050
Obesity		4(8.00)	0(0.00)	1.89	1.68

N: Number**; SD:** Standard Deviation; U**:** Mann Whitney test**;** χ^2**:** Chi-square test**; ADHD:** Attention deficit hyperactivity disorder; *Significant

The ALT level was significantly higher in the autistic group than controls (p=0.032). Additionally, IQ level was significantly lower in the autistic group than controls (p=0.001) **(Table 2)**.

Table (2): Laboratory investigations among the studied groups.

Studied variables	Autistic group (N=50)	Control group (N=50)	t-test	P value
Serum Calcium (mg/dl): Mean ±SD	10.0±0.65	10.1 ±0.54	0.870	0.389
ALT(IU/L): Mean ±SD	22.3±4.12	18.7±3.48	2.21	**0.032***
AST(IU/L): Mean ±SD	24.6±4.88	21.2±5.72	1.74	0.087
IQ level: Mean ±SD	84.2±13.6	102.0 ±6.69	5.85	**<0.001***

ALT: Alanine transaminase; AST: Aspartate transaminase; IQ: Intelligence quotient; *Significant.

A significant difference was observed between the studied groups regarding gross motor, fine motor, and social development (p<0.001) **(Table 3)**.

Table (3): Clinical data of the studied groups.

Studied variables	Autistic group (N=50)		Control group (N=50)		χ^2	P value
	No.	%	No.	%		
Head support:						
Normal	18	36.0	42	84.0		
Delayed	32	64.0	8	16.0	24.0	**<0.001***
Social smile:						
Normal	4	8.00	50	100		
Delayed	64	92.0	0	0.00	85.1	**<0.001***
Crawling:						
Normal	4	8.00	50	100		
Delayed	64	92.0	0	0.00	85.1	**<0.001***
Teething:						
Normal	28	56.0	50	100		
Delayed	22	44.0	0	0.00	21.9	**<0.001***
Sitting:						
Normal	30	60.0	42	84.0		
Delayed	20	40.0	8	16.0	7.14	**0.008***
Walking:						
Normal	2	4.00	48	96.0		
Delayed	48	96.0	2	4.00	84.6	**<0.001***
Knowing mother:						
Normal	8	16.0	46	92.0		
Delayed	42	84.0	4	8.00	58.1	**<0.001***
Reaction to stranger:						
Normal	4	8.00	46	92.0		
Delayed	46	92.0	4	8.00	70.5	**<0.001***
Eye contact:						
Normal	0	0.00	50	100	92.1	**<0.001***
No response	20	40.0	0	0.00	21.1	**<0.001***
Fair	12	24.0	0	0.00	10.6	**0.001***
Poor	18	36.0	0	0.00	18.7	**<0.001***
Obey simple order:						
Yes	2	4.00	50	100		
No	48	96.0	0	0.00	92.3	**<0.001***
Delayed Speech:						
Yes	44	88.0	4	8.00		
No	6	12.0	46	92.0	64.1	**<0.001***
CARS:						
Mean ±SD	37.1±5.16		---		---	---
Median	38.0					
Range	30.0 – 47.5					

*****Significant.

The genotypic and allelic frequencies of *rs 2162600 T /C* of *SCN1A* gene and rs *2304016 A/G* of *SCN2A* gene were found to follow the Hardy–Weinberg equilibrium **(Table 4)**.

Table (4): Genotyping and allele distribution SCN1A rs 2162600 and SCN2A rs 2304016 genes polymorphism among the studied groups.

Variables	Autistic group (No=50)		Control group (N=50)		OR 95%CI	P value
	No.	%	No.	%		
SCN1A rs 2162600						
TT	34	68.0	40	80.0	Reference	
TC	12	24.0	8	16.0	0.56(0.20 – 1.57)	0.267
CC	4	8.00	2	4.00	0.42(0.07 – 2.46)	0.340
HWE	0.164		0.086			
Alleles	N=100		N=100			
T	80	80.0	88	88.0	Reference	0.126
C	20	12.0	12	12.0	0.54(0.25 – 1.18)	
SCN2A 2 rs 2304016						
AA	42	84.0	46	92.0	Reference	
AG	7	14.0	4	8.00	0.52(0.14 – 1.91)	0.983
GG	1	2.00	0	0.00	0.30(0.01 – 7.68)	0.470
HWE	0.304		0.768			
Alleles	N=100		N=100			
A	91	91.0	96	96.0	Reference	
G	9	9.00	4	4.00	0.42(0.12 – 1.41)	0.162

HWE; Hardy-Weinberg equilibrium; **OR**; Odds ratio; CI; Confidence interval; *Significant

Regarding *SCN1A rs 2162600*, the frequency of CC and CT genotypes was higher in the autistic group in comparison with controls. In addition, the TT genotype was higher in controls compared to the autistic group. However, these differences did not reach statistical significance. Concerning *SCN2A rs 2304016*, genotype and allele distribution did not show significant differences (p>0.05). Multivariate logistic regression analysis revealed that maternal age is an independent predictor of autism among the studied group, as the increase in mother age increases the risk for autism **(Table 5)**.

Table (5): Univariate and multivariate regression analysis for independent predictors of autism among the studied groups.

Studied variables	Univariate	P value	Multivariate	P-value
	OR 95%CI		OR 95%CI	
Order of birth:				
1st +2nd	Reference		-	-
3rd	1.93(0.62 – 6.05)	0.254		
Maternal age (years):	0.36(0.22 – 0.57)	**0.001***	0.35 (0.22 – 1.19)	**0.001***
Prenatal complications:				
No	Reference	0.654		
Gestational diabetes	1.32(0.88 – 3.45)		-	-
Postnatal complications:				
No	Reference		Reference	
Delayed crying	2.66(1.09 – 6.52)	**0.032***	1.16(0.033 – 1.19)	0.077
Type of feeding:				
Breastfeeding	Reference			
Artificial feeding	1.12(0.85 – 3.20)	0.432		
Co-morbidities:				
No	Reference		-	-
ADHD	1.22(0.65 – 2.12)	0.212		
SCN1A rs 2162600:				
TT+TC	Reference		-	-
CC	0.55(0.293 – 1.05)	0.074		
SCN2A rs 2304016:				
AA	Reference		-	-
AG+GG	0.44(0.136 – 1.46)	0.184		

*Significant.

DISCUSSION

Autism is a neurobiological disorder determined by both hereditary and environmental variables influencing the brain and including risk factors for ASD [15]. The creation and transmission of action potential within neurons is facilitated by proteins called neuronal voltage-gated sodium channels. This happens by promoting ion diffusion down an electrochemical gradient to the sodium equilibrium potential and increasing the membrane's permeability to sodium ions [15].

In the current study, there was male predominance with the highest incidence in the 1st birth order child.

This agreed with the findings of **Galvan *et al.*** [16] who found in their research that first-born kids seem to be more susceptible to ASD than later-born children. In the present study, a significant difference was observed in prenatal and postnatal data of the studied group regarding maternal age, family history for comorbidities, gestational hypertension, and delayed crying. The mothers of children with ASD were older than the mothers of controls.

Moreover, **Larsson *et al.*** [17] stated that ASD children were more likely to be male and to have mothers aged ≥30 years. Regarding family history for comorbidities, we found that the autistic group had a positive family history of ADHD, epilepsy, and obesity, while controls had no family history of comorbidities. Furthermore, gestational hypertension was higher in mothers of children in the autistic group. However, **Surén *et al.*** [18] indicated that a higher incidence of autism was associated with paternal obesity (BMI > 30) and Asperger disorder, whereas mother obesity (BMI > 30) was only marginally connected with ASD risk. Children of obese fathers had a greater risk of developing autism than children of normal-weight fathers.

On the contrary, **Gardener *et al.*** [19] claimed that there is inadequate evidence to link anyone's prenatal condition to the etiology of autism and that pre-eclampsia, hypertension, and edema have a non-significant connection with ASD. Differences in lifestyle and environmental factors can be used to explain this.

In the current study, delayed crying at birth was found significantly higher in the autistic group than controls. However, **George *et al.*** [20] found that there was no proof that the absence of crying at delivery was associated positively with ASD.

In addition, **Maramara *et al.*** [21] demonstrated that delayed crying could be linked to further newborn respiratory problems, including hypoxia and difficulty beginning breathing. These factors can be the result of several prenatal conditions and birth circumstances that, at birth, may result in issues with diminished oxygen levels in the brain.

In addition, **Duan *et al.*** [22] revealed that dopaminergic hyperactivity in some children with ASD has been attributed to anoxia caused by hypoxia at birth, which may enhance the dopaminergic system. The results of this study illustrated that ALT level was significantly higher in the autistic group than in controls. However, serum Ca and AST did not show significant differences.

These results partially agreed with those of **Karim *et al.*** [23] who stated that the mean serum AST and ALT levels in autistic children were significantly more than those in normal children.

On the contrary, **Shahjadi *et al.*** [24] revealed that serum calcium levels in children with ASD were considerably lower in comparison with controls who found that the mean values of serum AST and ALT were significantly elevated in autistic children compared to controls.

In this study, we found that IQ level was significantly lower in the autistic group than controls.

A study by **Charman *et al.*** [25] indicated that out of 75 children with ASD, 55% had intellectual disabilities (IQs below 70), while only 16% had moderate to severe intellectual disabilities (IQs below 50), and 28% had average intelligence (IQs between 115 and 85, but not above), with only 3% having IQs above 115. The findings of this investigation revealed a considerable difference between the investigated groups in terms of their clinical data (gross motor, fine motor, and social development). Delayed head support and delayed walking were significantly more present in the autistic group.

In accordance with these results, **Flanagan *et al.*** [26] found that siblings of children with ASD were more likely to experience head lag than low-risk newborns at the age of 6 months. Additionally, there is a significantly higher number of infants who were diagnosed with ASD than those who did not show signs of head lag.

In contrast, **Bishop *et al.*** [27] demonstrated that children with ASD were less likely to have delayed walking than those without ASD diagnosis and that this difference was greater at lower IQ levels. This discrepancy can be accounted for by variations in sample size and environmental variables.

In the current study, *rs 2162600 T/C* of *SCN1A* gene and *rs 2304016 A/G* of *SCN2A* gene were investigated to study their role in ASD. The incidence of CC and CT genotypes of *rs 2162600* was elevated in the autistic group in comparison with the control group. However, this did not reach statistical significance. Meanwhile, no significant difference was observed regarding *rs 2304016* genotype and allele distribution between the studied groups. The SCN1A gene region on chromosome 2q24.3 has been identified as an autism susceptibility locus by genome-wide association studies.

In the study of **Han *et al.*** [28] who sequenced the genomes of ASD patients, identified mutations of *SCN1A* gene in familial autism. Dravet's syndrome, a pediatric neuropsychiatric condition characterized by recurring intractable seizures, cognitive deficiency, and behaviors on the autistic spectrum, is brought on by haploinsufficiency of the SCN1A gene, encoding the voltage-gated sodium channel NaV1.1.

Furthermore, **O'Roak *et al.*** [29] stated that proband 12499 was found to have a missense mutation at a highly conserved location in SCN1A that is likely to be functionally damaging. The condition severity was indicated by the subject's (CSS 8) early onset, probable regression, linguistic delay, and epilepsy diagnosis. SCN1A has previously been linked to epilepsy and has been proposed as a potential gene for ASDs.

Moreover, **Craig *et al.*** [30] found that in addition to causing biopsy-proven mitochondrial illness, SCN1A alleles are known to produce the phenotypes of autism and epilepsy.

It was particularly interesting that the seizure alleles differ significantly from the SCN1A alleles linked to autism, resulting in more severe damage to the channel protein. SCN1A alleles linked to autism disrupt the channel protein's intracellular calmodulin-interacting regions. These areas link this sodium channel to the calcium signaling pathways of the neuron because they interact with calmodulin, serving as an actual binding protein subunit of channel [31].

However, SCN2A is different from other ASD-related genes in several significant ways. First, voltage-gated sodium channels are primarily expressed in the axon, whereas most of the genes linked to ASD are either involved in chromatin control or synapse assembly. Second, SCN2A exhibits a pattern uncommon in any other gene, including an excess of de novo missense mutations in addition to de novo protein-truncating variants (PTVs). Finally, genetic variations in SCN2A have been linked to infantile seizures in the past, including epileptic encephalopathy (EE) with poor developmental outcomes and benign infantile familial seizures (BIFS). Gain-of-function mutations are the most common type of SCN2A missense variant linked to infantile seizures in BIFS and EE. ASD/developmental delay mutations are either missense mutations with uncertain effects or PTVs causing sodium channel function to be lost [32].

The neuronal paralogs of the alpha subunit, SCN1A and SCN2A, have been linked to alterations in genetic epilepsy that also involves febrile episodes. Additionally, it was shown that SCN1A carries haplo-insufficient dominant null alleles in the Dravet syndrome and severe myoclonic epilepsy of infancy (SMEI) along with missense alleles in the familial hemiplegic migraine syndrome [33].

In the study of **Weiss *et al.*** [34] a susceptibility locus for autism was discovered on chromosome 2 close to a set of voltage-gated sodium channel genes. The seizure disorder GEFS+ is brought on by mutations in the SCN1A and SCN2A genes. They examined 117 multiplex autism families for variations in coding exons and splice sites, and they discovered that one autism family had R542Q in SCN1A, which had previously been detected in a patient with juvenile myoclonic epilepsy.

Furthermore, **Lu *et al.*** [35] demonstrated that rs 2162600 (SCN1A), among other SNPs, was linked to VPA responsiveness in Chinese Han patients with epilepsy. These gene alterations have been shown to have the ability to influence medication reactions, allowing for more customized VPA treatment for epileptic patients.

SCN2A, one of the genes most often altered in these neuropsychiatric diseases, was revealed to be responsible for 0.5% of patients with ASD, 1.4% of those with epileptic encephalopathy, 2.3% of those with intellectual disability, and 0.1% of those with schizophrenia [35].

The results from various studies may differ due to multiple variables, such as altering disease susceptibility, variations in ethnic background, and various study methodologies. This might also suggest that other genes contribute to the development of ASD. The study's single-center design and limited sample size could have an impact on the findings. Therefore, to verify our findings, additional multi-center studies with a higher sample size are required.

CONCLUSIONS

The frequency of CC genotype of SCN1A rs 2162600 was higher in the autistic group. However, this did not reach statistical significance. Moreover, no significant difference was observed regarding SCN2A rs 2304016 genotype and allele distribution between the studied groups. Maternal age was an independent risk factor for autism among the studied group.

No funding.
No conflict of interest.

REFERENCES

1. **Ozonoff S, Iosif A, Baguio F *et al.* (2010):** A prospective study of the emergence of early behavioral signs of autism. Journal of the American Academy of Child & Adolescent Psychiatry, 49(3): 256-266.
2. **Lukmanji S, Manji S, Kadhim S *et al.* (2019):** The co-occurrence of epilepsy and autism: A systematic review. Epilepsy & Behavior, 98: 238-248.
3. **Botelho R, Silva A, Borbely A (2024):** The Autism Spectrum Disorder and Its Possible Origins in Pregnancy. International Journal of Environmental Research and Public Health, 21(3): 244. DOI: 10.3390/ijerph21030244
4. **Noriega D, Savelkoul H (2014):** Immune dysregulation in autism spectrum disorder. European Journal of Pediatrics, 173: 33-43.
5. **Breuss M, Antaki D, George R *et al.* (2020):** Autism risk in offspring can be assessed through quantification of male sperm mosaicism. Nature Medicine, 26(1): 143-50.

6. **Zaki R, Moawad G (2016):** Influence of autism awareness on the psychological well-being of mothers caring for their children with autism. Journal of Nursing Education and Practice, 6(9): 90-100.
7. **Sundari F, Supena A (2022):** Efforts to Teach Social Interaction to Autism Students in Inclusive Elementary Schools. Pedagonal: Jurnal Ilmiah Pendidikan, 6(1):1-12.
8. **Xi T, Wu J (2022):** A review on the mechanism between different factors and the occurrence of autism and ADHD. Psychology Research and Behavior Management, 14: 393-403.
9. **Ademuwagun I, Rotimi S, Syrbe S *et al.* (2021):** Voltage gated sodium channel genes in epilepsy: Mutations, functional studies, and treatment dimensions. Frontiers in Neurology, 12: 600050. DOI: 10.3389/fneur.2021.600050
10. **Malcolm J, Sajjaboontawee N, Yerlikaya S *et al.* (2023):** Voltage-gated sodium channels, sodium transport and progression of solid tumours. Current Topics in Membranes, 92: 71-98.
11. **Rodrigues T, de Moura J, dos Santos A *et al.* (2023):** Epileptic Targets and Drugs: A Mini-Review. Current Drug Targets, 24(3): 212-24.
12. **Daghsni M, Rima M, Fajloun Z *et al.* (2018):** Autism throughout genetics: Perusal of the implication of ion channels. Brain and Behavior, 8(8): e00978. DOI: 10.1002/brb3.978
13. **Meisler M, Hill S, Yu W (2021):** Sodium channelopathies in neurodevelopmental disorders. Nature Reviews Neuroscience, 22(3): 152-166.
14. **Lindy A, Stosser M, Butler E *et al.* (2018):** Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders. Epilepsia, 59(5): 1062-1071.
15. **Ghazala E, Shahin D, Wahba Y (2022):** Polymorphisms of the sodium voltage-gated channel, alpha subunit 1 (SCN1A-A3184G) gene among children with non-lesional epilepsy: A case-control study. Italian Journal of Pediatrics, 48(1): 157. DOI: 10.1186/s13052-022-01352-9
16. **Galvan J, Ramalingam P, Patil S *et al.* (2020):** Mode of delivery, order of birth, parental age gap and autism spectrum disorder among Malaysian children: A case-control study. Heliyon, 6(10): e05068. DOI: 10.1016/j.heliyon.2020.e05068
17. **Larsson H, Eaton W, Madsen K *et al.* (2005):** Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. American Journal of Epidemiology, 161(10): 916-925.
18. **Surén P, Gunnes N, Roth C *et al.* (2014):** Parental obesity and risk of autism spectrum disorder. Pediatrics, 133(5): 1128-1138.
19. **Gardener H, Spiegelman D, Buka S (2009):** Prenatal risk factors for autism: comprehensive meta-analysis. The British Journal of Psychiatry, 195(1): 7-14.
20. **George B, Padmam M, Nair M *et al.* (2014):** CDC Kerala 13: antenatal, Natal and postnatal factors among children (2–6 y) with autism–a case control study. The Indian Journal of Pediatrics, 81: 133-137.
21. **Maramara L, He W, Ming X (2014):** Pre-and perinatal risk factors for autism spectrum disorder in a New Jersey cohort. Journal of Child Neurology, 29(12): 1645-1651.
22. **Duan G, Yao M, Ma Y *et al.* (2014):** Perinatal and background risk factors for childhood autism in central China. Psychiatry Research, 220(1-2): 410-417.
23. **Karim M, Begum S, Shahzadi S (2016):** Serum lactate, AST, ALT in male autistic children in Bangladesh. Journal of Bangladesh Society of Physiologist, 10(2): 56-60.
24. **Shahjadi S, Khan A, Ahmed M *et al.* (2020):** Study On Serum Magnesium, Calcium And Iron In Autism Spectrum Disorder (ASD) Children. Journal of Dhaka Medical College, 27: 199-204.
25. **Charman T, Pickles A, Simonoff E *et al.* (2011):** IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). Psychological Medicine, 41(3): 619-627.
26. **Flanagan J, Landa R, Bhat A *et al.* (2012):** Head lag in infants at risk for autism: a preliminary study. The American Journal of Occupational Therapy, 66(5): 577-585.
27. **Bishop S, Thurm A, Farmer C *et al.* (2016):** Autism spectrum disorder, intellectual disability, and delayed walking. Pediatrics, 137(3): e20152959. DOI: 10.1542/peds.2015-2959
28. **Han S, Tai C, Westenbroek R *et al.* (2012):** Autistic-like behaviour in Scn1a+/− mice and rescue by enhanced GABA-mediated neurotransmission. Nature, 489(7416): 385-390.
29. **O'Roak B, Deriziotis P, Lee C *et al.* (2011):** Exome sequencing in sporadic autism spectrum disorders identifies severe novo mutations. Nature Genetics, 43(6): 585-589.
30. **Craig A, de Menzes M, Saneto R (2012):** Dravet syndrome: Patients with co-morbid SCN1A gene mutations and mitochondrial electron transport chain defects. Seizure, 21(1):17-20.
31. **Schmunk G, Gargus J (2013):** Channelopathy pathogenesis in autism spectrum disorders. Frontiers in Genetics, 4: 222. DOI: 10.3389/fgene.2013.00222
32. **Schwarz N, Hahn A, Bast T *et al.* (2016):** Mutations in the sodium channel gene SCN2A cause neonatal epilepsy with late-onset episodic ataxia. Journal of Neurology, 263: 334-343.
33. **Tapia A, Giachello C, Palomino-Schätzlein M *et al.* (2021):** Generation and characterization of the Drosophila melanogaster paralytic gene knock-out as a model for dravet syndrome. Life, 11(11): 1261. DOI: 10.3390/life11111261
34. **Dichgans M, Freilinger T, Eckstein G *et al.* (2005):** Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. The Lancet, 366 (9483): 371-377.
35. **Lu Y, Su Q, Li M *et al.* (2020):** Association of SCN1A, SCN2A, and UGT2B7 polymorphisms with responsiveness to valproic acid in the treatment of epilepsy. BioMed Research International, 20(1): 8096235. DOI: 10.1155/2020/8096235