J Human Gen Genom. 2021 December; 5(1): A-10-307-2 doi: 10.52547/jhgg.5.1.70
Published online 2022 October 18. Research Article

Expression deregulation of SHANK3 gene in children with autism spectrum disorder and attention deficit and hyperactivity disorder

Hanieh Bai[1], Seyed Yousef Seyedena[1], Morteza Karimipoor[2], Mehrdad Hashemi[3,4]*

1 Department of Biology, Faculty of Biological Sciences, Islamic Azad University, North Tehran Branch, Tehran, Iran
2 Molecular Medicine department, Biotechnology Research Center, Pasteur Institute of Iran, Tehran, Iran
3 Department of Genetics, Faculty of Advanced Science, Islamic Azad University, Tehran, Iran
4 Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital, Tehran, Iran

*Corresponding author: Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital, Tehran, Iran.
Email: drmehashemi@gmail.com
Received 2022 May 10; **Revised** 2022 June 12; **Accepted** 2022 June 18.

Abstract

Background: Autism spectrum disorder (ASD) is a complicated neurodevelopmental disease with a social communication disorder, language problems, restricted, repetitive patterns, and patterns of behavior, activities, and interests. Attention deficit hyperactivity disorder (ADHD) is a pediatric psychiatric disorder with symptoms including attention deficit, hyperactivity, and impulsiveness, which can persist into adulthood. The SHANK gene family encodes Shank proteins, which are multidomain scaffold proteins involved in the binding of the postsynaptic density in neurotransmitter receptors, ion channels, and several G-protein-coupled signaling pathways. SHANK3, also known as proline-rich synapse-associated protein 2 (ProSAP2), is a protein encoded by the SHANK3 gene located in human chromosome 22, which plays an essential role in synapse formation, spine maturation, and scaffold activity.
Objectives: In the present study, the expression level of SHANK3 in ASD and ADHD patients was assessed. Method: mRNA levels of the SHANK3 were evaluated in the peripheral blood of 450 unrelated ASD patients and 450 unrelated ADHD patients. The control group included 490 unrelated non-psychiatric children by quantitative RT-PCR. In addition, gene expression and its correlation with clinical symptoms were examined.
Results: The results showed mRNA level of the SHANK3 gene was significantly down-regulated in ASD patients vs. normal children. In ADHD, a significant reduction of SHANK3 expression was also detected compared to normal children.
Conclusions: The SHANK family, especially the SHANK3 gene, may play an essential role in the etiology of ASD and ADHD. Findings also may reveal a shared genetic basis in two neurodevelopment disorders related to synaptic pathways.

Keywords: SHANK3, ASD, ADHD, quantitative PCR.

Introduction

Autism spectrum disorder (ASD) and attention deficit and hyperactivity disorder (ADHD) are two neuropsychiatric and neurodevelopmental disorders with solid evidence of the involvement of genetic factors in both disorders. ASD is characterized by severe social and communication deficiencies and language impairments. ASD appears by age three, and it is estimated that the prevalence of the disorder is 1 in every 57 children in the United States (1). ADHD is characterized by inattention, hyperactivity, impulsivity, and motivational/emotional deregulation (2). Several lines of evidence suggest that ASD and ADHD pathophysiology may relate to structural and functional abnormalities in the central nervous system (3). Several candidate genes and genetic risk factors, such as single nucleotide polymorphisms and copy number variations, were associated with ASD and ADHD. Due to the shared clinical appearances of ASD and ADHD, the shared genetic bases of these disorders became a hot topic (4). Synaptic molecules, including proteins involved in localized pre-synaptic and postsynaptic proteins, are involved in the maturation and function of glutamatergic synapses (5). The Neurexins (Nrxns) family is responsible for pre-synaptic functions. The Neuroligin (NLGN) family in postsynaptic membrane protein has an essential role in forming and

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[DOI: 10.52547/jhgg.5.1.70]

Several studies have found associations between dysfunctions in these genes. Their genotype variants and cognitive abnormalities in psychiatric disorders such as ASD (8, 9) and schizophrenia (10) have been reported, While Nrxn/Login complex abnormalities have been reported in neurodevelopmental disorders. The SHANK gene family, including SHANK1, SHANK2, and SHANK3, have been implicated as causative and promising candidates for ASD. (11) Shank proteins are synaptic scaffolding proteins that orchestrate a protein complex at the postsynaptic density (PSD).

Many of genes implicated in the development of ASD encode proteins that are crucial components of excitatory glutamatergic synapses, including ProSAP1/Shank2, ProSAP2/Shank3, Neuroligins, Neurexins, SAPAP2 (DLGAP2) from the GKAP/SAPAP family of ProSAP/Shank interacting proteins, as well as Cadherins, Contactin Contactin-associated protein and other cell-adhesion molecules (CAMs), calcium channels, and neurotransmitter receptors. (12) While Shank 1 and 2 share a similar protein domain structure with Shank 3, each gene has a different expression pattern and cellular localization (13,14).

Several studies have shown similarities between ASD and ADHD, including structural and functional abnormalities of the brain, as well as poor social skills, attention problems, and language impairments (15,16). The present study aimed to evaluate the mRNA level of the SHANK3 gene in the peripheral blood of ASD and ADHD children compared to the control group of healthy children to study the association between SHANK3 expression alteration and ASD and ADHD, which might provide insight into the pathogenic mechanisms of these disorders.

Material and methods:

Sampling:

The study included 450 unrelated ASD children, 260 males (58%), 190 females (42%) with a mean age of 8.2±1.3 years), 450 unrelated ADHD children (250 males (55%), 200 females (45%) with a mean age of 8.4±1.8 year), and the control group included 490 unrelated normal control children (245 males (50%), 245 females (50%) with a mean age of 9.1±3.1 year). Two independent psychiatrists investigated patients through unstructured or semi-structured behavioral observations in children and interviews with children, their parents, and teachers based on DSM-V criteria. Children with IQ scores lower than 70 were excluded from the study. ADHD and ASD samples were diagnosed early, and no treatment was started at the time of participation. Patients have been recruited from the outpatient psychiatric clinics of 18 provinces of Iran. Non-psychiatric subjects were recruited from mental health children who received regular medical checkups before school enrolment in local medical centers with no history of psychological or somatic symptom disorder. All three groups were matched on sex, age, race, socioeconomic situation, and familial situation. Tables 1A,1B, and 2 present demographic, clinical, and statistical data. Individuals with combined ASD and ADHD were excluded from the study. None of the subjects or their parents had a current history of a severe medical condition, neurological disorder, history of traumatic brain injury with loss of consciousness, any psycho-stimulant or opioid drug abuse, or alcohol or nicotine dependence. Parents were provided information about the study's purpose and informed consent. Children were verbally told about the study. The study was reviewed and approved by the central ethical committee of Islamic Azad University, Tehran, Iran.

Blood sampling and RNA extraction:

In tubes containing EDTA, five ml of peripheral blood was obtained from the cubital vein without a tourniquet between 10.00 and 11.00 AM. Total RNA was extracted from peripheral blood samples immediately after samplings using an RNA Purification kit (GeneJET™ RNA Purification Kit#K0732, Thermo scientific - Fermentas, Latvia) according to manufacturer instructions. To avoid any genomic DNA contamination, extracted RNA was treated with RNase-free DNase I enzyme (Fermentas, Latvia), based on the kit protocol. The quality and quantity of RNA were assessed using agarose gel electrophoresis and a spectrophotonanometer.

cDNA synthesis:

cDNA was synthesized by RevertAid Premium First Strand cDNA First Strand cDNA Synthesis Kit (#K1652, Thermo scientific-Fermentas, Latvia) according to the manufacturer's protocol.

Real-time PCR:

Specific primers were designed by "oligo7" software and were blasted on the NCBI website. The Phosphoglycerate Kinase 1 (PGK1) gene was used for normalization as an internal control gene. Primers were provided in table 3. Quantitative PCR was performed by using SYBR green (Thermo Scientific Maxima SYBR Green/ROX qPCR Master Mix (2X) #K0221, Thermo scientific - Fermentas, Latvia) with 0.3 μM concentration forward and reverse primers (10 Pmol), and cDNA (up to 400 ng/25 μl reaction). CFX96 Touch Real-Time PCR Detection System (BIO-RAD, California, US) used for triplicate method Quantitative Real Time-PCR. The pfafle formula was used to calculate the fold changes.

Statistical analysis:

Descriptive data are expressed as mean ± SD (range), and the level of statistical significance was set at P-value less than 0.05. The Kolmogorov-Smirnov test assessed compliance with normal distribution for continuous variables. Statistical differences were calculated by one-way ANOVA followed by independent Student's t-test for multiple group comparisons. The Pearson correlation exam was performed to determine the relationship between variables. The Bonferroni correction test performed multiple comparison corrections. SPSS software version 24 was used for statistical analysis.

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Results:

gene expression evaluation:

Real-time PCR data revealed that the mRNA level of the SHANK3 gene was significantly down-regulated in the ASD group compared to normal children. In ADHD subjects, significant downregulation of SHANK3 was also revealed compared to normal children. The Comparison of ASD and ADHD subjects showed no significant difference between ASDs and ADHD for SHANK3. Details of p-values and expression ratio for each gene have been shown showing in table 4. No significant correlation was identified between SHANK3 mRNA level and age, age of onset, and duration of illness. Figure1 shows a boxplot defining the comparison of gene expression between the three studied groups.

Sex effects evaluation:

Effects of gender in the SHANK3 expression level were assessed in all participants. No significant difference was found when we separated all subjects into two groups, including 755 boys and 635 girls. In ASD children, significant downregulation of SHANK3 was shown in boys compared to girls (P value= 0.004). In addition, in the ADHD children, the mRNA level of SHANK3 was significantly lower in boys compared to girls (P value= 0.003).

Discussion:

Gene expression findings have shown that the low mRNA level of the SHANK3 gene may be considered a potential marker for ASD and ADHD. Proteins of the postsynaptic density in excitatory synapses have a significant role in the etiology of psychiatric disorders. Previous studies showed variants in the three SHANK genes encoding postsynaptic scaffolding proteins have been associated with autism spectrum disorders and ADHD (17). Alteration in excitatory/inhibitory balance and involved genes in this balance have been reported in neurodevelopmental disorders like autism and schizophrenia (18). Human cell line studies revealed morphological changes on primary hippocampal neurons and the effect on actin polymerization in fibroblast cell lines as a consequence of upregulation and/or knockdown-rescue of the SHANK3 gene. SHANK expression deregulation also may cause alterations in spine density and clustering at synapses along with an overall loss of presynaptic contact that, in turn, cause functional impairment (19). Dopaminergic neuron dysfunction is also essential in the etiology of neurodevelopment disorders, including ADHD, that may lead to striatum activation reduction and low functioning of reward circuits (20, 21). It has been reported that SHANK3 controls the maturation of social reward and the main dopamine circuits in the ventral tegmental area (VTA). Dysfunctions in associative learning caused by SHANK3 insufficiency in ASD and ADHD children (22). Intact excitability and expression of the ASD-associated proteins, such as NLGN3 and SHANK3, at dopaminergic neurons of VTA may lead to learning disability and impulsivity (23). Previous reports, including functional and genotyping analysis, approved the roles of SHANK3 in numerous higher brain functions (24). It has been known that autistic behavior, significant developmental delay, and severe speech and language deficit in Phelan- McDermid syndrome or 22q13.3 deletion syndrome is caused by deletion and loss of function or downregulation of the SHANK3 gene. (25) In addition, cumulative gene analysis in autistic cases has detected several mutations in the SHANK3 gene, comprising deletion and duplications related to the neuropathology of autism spectrum disorder (ASD). Our findings and gene ontology studies on the effect of SHANK3 expression compared with behavioral studies of SHANK3-mutant mice may provide evidence about the SHANK3 role in ASD and ADHD and even could suggest novel therapeutic approaches for this disorder (26).

Neurodevelopmental psychiatric disorders are multigenic and multifactorial heterogeneous disorders. Involvement of dopaminergic pathways, mitochondrial and respiratory complexes (27), immune systems (28), neuron pruning, and transcription factors (29), and recently synaptogenesis was reported in several psychiatric disorders, including ASD and ADHD. Pathways related to pre-synapse, post-synapse, and maintenance of synapse may shed light on the brain function and the etiology of ASD and ADHD, along with similarities and differences between these disorders. Finding altered gene expression patterns and novel biomarker detection, such as altered SHANK3 expression patterns in ASD and ADHD disorders, might provide insight into advancing effective diagnostics and intervention strategies in both diseases.

Acknowledgements
I would like to thank all those who collaborated and supported me in the process of this study.

Conflict of interest: One of the authors of this article is a member of the committee board of the Journal of Human Genetics and Genomics.

Funding support: Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital, Tehran, Iran.

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Tables:

Table 1. (part A): Basic demographic data of each group.

Variable	Autism spectrum disorder	Attention deficit and hyperactivity disorder	Control children
Sex	260 male,190 female	250 male,200 female	245 male, 245 male
Age	8.2±1.3	8.4±1.8	9.1±3.1
Body mass index	19±2.3	20±3.1	20±3.6
Race	85% Caucasian/15% other	88% Caucasian/12% other	83% Caucasian/17% other
Education (who didn't went to School)	17	21	11

Table 1. (part B): Non-significant p-value in the basic demographic situation between groups.

Variable	Autism spectrum disorder vs. control children	Attention deficit and hyperactivity disorder vs. control children	Autism spectrum disorder vs. Attention deficit and hyperactivity disorder
Sex	p = 0.55	p = 0.33	p = 0.31
Age	p = 0.49	p = 0.29	p = 0.41
Body mass index	p = 0.77	p = 0.18	p = 0.37
Race	p = 0.62	p = 0.32	p = 0.48
Socioeconomic situation	p = 0.58	p = 0.5	p = 0.29
Familial situation	p = 0.49	p = 0.53	p = 0.43
Education	p = 0.84	p = 0.44	p = 0.76

Table 2. Psychological and clinical variables (Means and Standard Deviations).

VARIABLE	ASD	ADHD	Normal
Age of onset	3.1±1.1	3.2±1.6	-
Illness time	6±3.1	5.2±1.5	-
IQ score	87.77±18.52	95.44±11.42	106.3±17.66

Table 3. sequences of primers used for Real-time PCR.

Genes primer	primer sequence	PCR product size (bp)
PGK1 forward primer	5'GTGCCAAATGGAACACGGAG3'	78
PGK1 reverse primer	5'TGCCAAGTGGAGATGCAGAA3'	
SHANK3 forward primer	5'GGGATCACCGACGAGAATGG3'	97
SHANK3 reverse primer	5'TGTCTGCCCCATAGAACAGC3'	

Table 4. P-value and Fold change of gene expression analysis between groups.

Gene	ASD vs. Normal	ADHD vs. Normal	ASD vs. ADHD
SHANK3	Fold change: 0.56 p value: 0.006	Fold change: 0.62 p value: 0.01	Fold change: 0.84 p value: 0.1

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Figure:

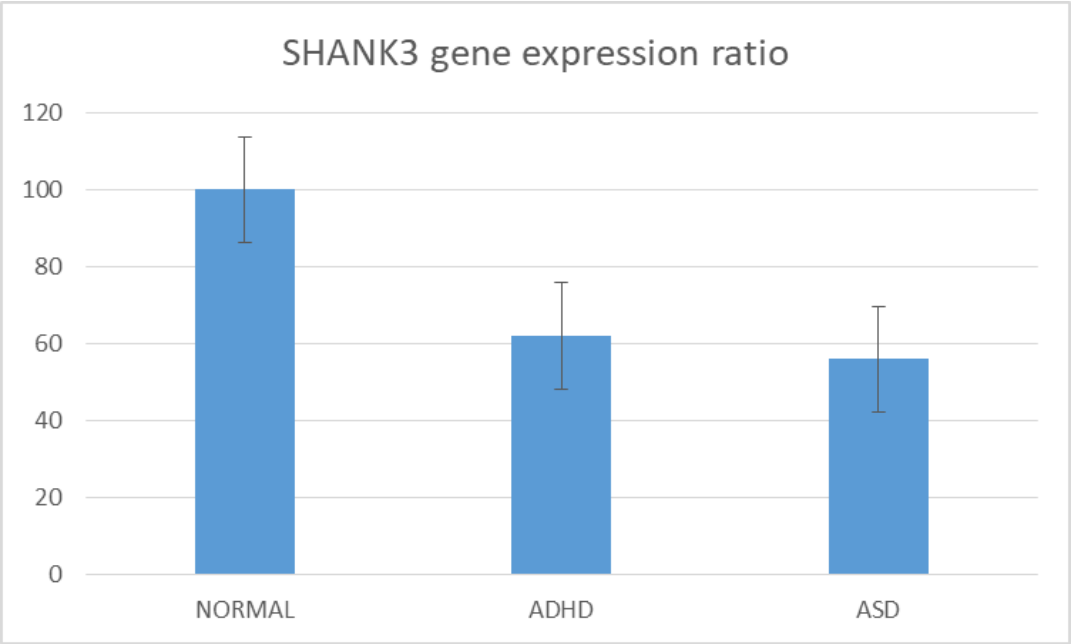

Figure 1 gene expression results of SHANK3 in three group of study showed that ASD group has lowest mRNA level and along with ADHD have down expressed compared with normal control children.

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