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The relationship of learning and memory disfunction with NEURL1 and RGS14 genes in patients with autism spectrum disorders

Otizm Spektrum Bozukluğu Olan Hastalarda Öğrenme ve Hafıza Bozukluklarının NEURL1 ve RGS14 Genleri ile İlişkisi

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ABSTRACT

Aim: We aimed to evaluate the relationship between learning-memory difficulties and NEURL1 and RGS14 genes in patients with autism spectrum disorders (ASD).
Method: Forty children with ASD (20 ASD, 20 high functioning autism (HFA)) and 20 healthy controls were enrolled in this study. NEURL1 and RGS14 gene expressions in blood samples of volunteers were assessed by quantitative Real-Time PCR (qRT-PCR). The clinical and demographical findings in patients were determined and examined in relation to the gene expressions.
Results: According to our findings, NEURL1 gene expression was decreased in both patient groups compared to the control ($p<0.05$). No significant difference between the groups in terms of the RGS14 gene ($p>0.05$). A statistically significant correlation was found between learning and memory difficulties and RGS14 gene expression in HFA patients ($p=0.045$). A positive correlation was observed between NEURL1 and RGS14 gene expressions of ASD patients ($p=0.032$, $r=0,59$).
Conclusion: In this study, we showed that the NEURL1 gene may affect learning and memory difficulties in ASD patients. Nonetheless, we recommend that both genes be studied with more patients and preferably with brain tissues. These genes were evaluated for the first time in a clinical study on autism, and we believe that they will contribute to the literature in this respect.

Keywords: Autism, Neuralized1, RGS14, Learning, Memory

ÖZ

Amaç: Bu çalışmada OSB hastalarında öğrenme ve hafıza güçlükleri ile NEURL1 ve RGS14 genleri arasındaki ilişkiyi değerlendirmeyi amaçladık.
Yöntem: Bu çalışmaya OSB'li 40 çocuk (20 OSB, 20 yüksek fonksiyonlu otizm (HFA)) ve 20 sağlıklı kontrol dahil edildi. Gönüllülerin kan örneklerinde NEURL1 ve RGS14 genlerinin ekspresyonları kantitatif Real-Time PCR (qRT-PCR) yöntemi ile değerlendirildi. Hastalardaki klinik ve demografik bulgular belirlenerek gen ekspresyonları ile ilişkisi incelendi.
Bulgular: Bulgularımıza göre her iki hasta grubunda da kontrol grubuna göre NEURL1 gen ekspresyonu azaldı ($p<0.05$). RGS14 geni açısından gruplar arasında anlamlı fark yoktu ($p>0.05$). HFA hastalarında öğrenme ve bellek güçlükleri ile RGS14 gen ekspresyonu arasında istatistiksel olarak anlamlı bir ilişki bulundu ($p = 0.045$). OSB hastalarının NEURL1 ve RGS14 gen ekspresyonları arasında pozitif korelasyon görüldü ($p=0.032$, $r=0,59$).
Sonuç: Bu çalışmada NEURL1 geninin OSB hastalarında öğrenme ve hafıza güçlüğünü etkileyebileceğini gösterdik. Ancak, her iki genin daha fazla hasta ve tercihen beyin dokuları ile çalışılmasını öneriyoruz. Bu genler ilk kez otizmle ilgili bir klinik çalışmada değerlendirilmiştir, bu açıdan literatüre katkı sağlayacağına inanıyoruz.

Anahtar Sözcükler: Otizm, NEURL1, RGS14, Öğrenme, Hafıza

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Introduction

Autism Spectrum Disorders (ASD) is a neurodevelopmental disorder characterized by cognitive and behavioural disorders that show its effect from an early age [1, 2]. There is wide clinical variability and heterogeneity in ASD. In this context, in addition to typical autism patients, a group of patients that have social interaction deficiencies and an Intelligence Quotient (IQ) of 70 and above, although they fulfil their cognitive functions, are defined as High Functioning Autism (HFA) [1, 4].

At present, the diagnosis of the disease is made based on the diagnostic criteria of the American Psychiatric Association DSM-V (5th edition) [3, 5]. It is known that individuals with ASD have abnormal cognitive episodic memory, difficulties with future planning, relatively weak memory and some learning disorders [6-8]. It is widely recognized that environmental factors, genetic and epigenetic factors are effective in the etiology of ASD. Although various genes associated with ASD have been identified in several studies, the risk genes that cause learning and memory disabilities in ASD have not been clear [1, 7].

The basic mechanism that regulates learning and memory is intercellular synaptic plasticity, which is characterized by a series of biochemical and physiological changes in neuronal synapses in the brain [9-11]. In recent years, it has been shown that Cytoplasmic Polyadenylation Element-Binding Proteins (CPEBs) regulate synaptic plasticity by modulating the poly-A tails of specific mRNAs, and accordingly, it is one of the regulatory elements of learning and memory [10-12]. An important point is that CPEB3 activity is regulated by Neuralized1 (NEURL1), which is an E3 ubiquitin ligase [13, 14]. It has been shown that CPEB3 and NEURL1 can be effective on learning and memory, through the study of post-mortem tissues of patients with ASD as well as in in vivo ASD models [11, 14-16]. CPEB3 is a negative regulator of Glu A1 and GluA2 are receptor of NMDA (N-metil-D-aspartat), although it has been demonstrated that NEURL1-mediated monoubiquitination of CPEB3 increases the translation levels of GluA1 and GluA2, and as a result, enhance learning and memory by increasing synaptic plasticity [11, 14, 17]. It is emphasized that this effect occurs because of overexpression of NEURL1. Therefore, the role of the NEURL1 gene in the pathogenesis of ASD may be significant [14].

On the other hand, it has been shown in previous studies that Regulator of G Protein Signaling 14 (RGS14), which is a member of the Regulators of G Protein Signaling (RGS) proteins gene family, is a suppressor of memory and hippocampal-based learning [18, 19]. In experimental studies, it has been shown that RGS14 regulates Long-Term Potentiation (LTP) and synaptic plasticity in the hippocampal area CA2, and this information has also been confirmed in human studies. The pre- and2 post-synaptic regulatory functions of RGS14 variants show that they have important roles in human neurophysiology and various neurological diseases. However, more studies are needed to fully elucidate the role of RGS14 [20].

In the present study, we aimed to examine whether there were differences in the expression levels of NEURL1 and RGS14 genes in blood samples of ASD, HFA patients and control groups. In our study, we expected that the NEURL1 gene would be downregulated and the RGS14 gene would be upregulated in ASD patients. We evaluated our results in terms of the relationship between learning and memory disorders and these genes. The NEURL1 and RGS14 genes were examined for the first time with ASD patients in this study.

Subjects and methods

Patient selection

Patients between the ages of two and sixteen diagnosed with ASD and HFA at the Child-Adolescent Psychiatry Clinic (Erciyes University) between 2013 and 2014, were included in this study. The sociodemographic data form and the Ankara Developmental Screening Inventory (ADSI) were used in patient selection by specialist psychiatrists, in accordance with DSM-V diagnostic criteria.

Patients using ASD-related drugs and patients with syndromic disorders were excluded. The patients who were included in the study were collected into two groups, ASD and HFA. Healthy individuals compatible with the age and gender of

the patients were selected for the control group. The number of the patients and control, therefore, consisted of sixty individuals in three groups of twenty.

RNA isolation and cDNA synthesis

The genetic examinations were conducted at Erciyes University Genome and Stem Cell Center (GENKOK). RNA extraction was performed using the High Pure RNA Isolation Kit (Roche Diagnostic, Version 12, Germany) from peripheral blood samples taken from participants in the study. The quality and quantity of the RNA were measured with nanodrop (Thermo Scientific, USA). The RNA samples were stored - 80^{0}C.

Complementary DNA (cDNA) synthesis was performed from the obtained RNAs using the Transcriptor High Fidelity cDNA Synthesis kit (Roche Diagnostics, GmbH, Mannheim). According to the manufacturer's instructions, the cDNA was synthesized by incubating for 10 minutes at 29ºC, 60 minutes at 48°C and 5 minutes at 85ºC (LabCycler Sensoquest, Göttingen, Germany). The PCR product was stored at -20^{0}C.

Gene expression analysis

Preamplification was performed to see the blood levels of target genes. For this step and in accordance with the manufacturer's guidelines, we used the Real Time Ready cDNA preamplification master mix (Roche Diagnostics, GmbH, Mannheim).

Neuralized1 and RGS14 mRNA expression levels were determined using the LightCycler®480 Real Time Ready Assay Master Probe Kit (Roche Diagnostics, GmbH, Mannheim) with the Semiquantitative Real-Time PCR (qRT-PCR) method. The protocol was performed in accordance with the manufacturer's guidelines. The primers sequences of the genes were as follows:

NEURL1, 5'-GACTCGGCTGTTATGCTGTTC-3' (F) and 5'-GAGCACCAGCTCGCTATCA-3' (R); RGS14 5'-AGGTCTACCTGGTGGGCAAT-3' (F) and 5'-GCACGGTGCAGTCCTGAT-3' (R); ACTB, 5'-TCCTCCCTGGAGAAGAGCTA-3' (F) and 5'-CGTGGATGCCACAGGACT-3' (R).

All samples were run in duplicate and means were used for statistics. Target genes were normalized with ACTB. The 2-ΔΔCT method was used to compare gene expression relative to quantification.

Statistical analysis

To compare the differences between the groups, either one-way analysis of variance (ANOVA) or the Kruskal-Wallis H test was used for continuous variables, according to the results of the normality test (Shapiro-Wilk Test); a chi-square analysis and frequency analysis was used for categorical variables. Spearman's test was used for correlation analysis and some variables, the list-based deletion method was used. The results were evaluated using the "SPSS 21.0 for Windows." A result of $p<0.05$ was considered statistically significant.

Results

The study included sixty individuals and of these, forty were patients (20 ASDs, 20 HFAs) and twenty were controls. In the study groups, there were 13 (65%) male and 7 (35%) female patients who were diagnosed with ASD, and of the patients who were diagnosed with HFA, 19 (95%) were male and 1 (5%) was female. The control group was comprised of 9 (45%) males and 11 (55%) females. There was a significant difference in terms of gender between the patient groups ($p=0.003$). The mean age of the patients with ASD diagnosis was 4.5±1.83 and the mean age of the patients diagnosed with HFA was 4.02±1.48, whereas the mean age of the control group was 4.2±1.8; there was a homogeneous distribution among the groups ($p=0.259$). When the patient groups were compared in terms of having an intellectual disability (ID), it was observed that 6 (30%) of the patients with ASD and 1 (5%) of the patients with HFA had ID, respectively ($p=0.037$). In addition, it was also determined that 5 (25%) of the parents of ASD patients who were included in the study had consanguinity. There was no sanguinity among the parents of the HFA patients ($p=0.017$). The relatives of 10 (50%) patients with ASD and 11 (55%) patients with HFA were found to have neurological diseases ($p=0.752$). The ADSI test was performed on each patient group and the result was observed to be abnormal in all ASD patients and in 11 (55%) of the HFA patients.

There was a statistically significant difference among the groups (p=0.001; p<0.05) (Table 1).

Table-1. The clinical and demographical findings in the study groups.

Variables	ASD (N=20)	HFA (N=20)	Control (N=20)	p value
Age (years)	4,5 ± 1,83	4,02 ± 1,48	4,22± 1,80	0.682
Gender				
Male	13 (65%)	19 (95%)	11(55%)	0.003*
Female	7 (35%)	1(5%)	9 (45%)	
ID	6 (30%)	1 (5%)	-	0.037*
Consanguinity	5 (25%)	0 (0%)	-	0.017*
Presence of Neurological Disease in Relatives	10 (50%)	11 (55%)	-	0.752
ADSI				
Abnormal	20(100(%)	11 (55%)	-	0.001*
Normal	0(%)	9(45%)	-	

ID: intellectual disability, ADSI: Ankara Developmental Screening Inventory, *p<0.05. (Mean ± SD).

Table-2. The gene expression results of the groups (Mean ± SD).

Groups	NEURL1	RGS14
Control	0,77±1,031	1,39±1,48
ASD	0,395±0,504	1,51±0,81
HFA	0,22±0,221	1,07±0,52
p Value	0,027*	0,219

*There is statistically significant (p < 0.05) difference between groups.

The gene expression results of the groups and the p values of the genes are shown in Table 2. NEURL1 gene expressions were significantly different between the groups (p<0.05). When NEURL1 gene expression was compared between the HFA and control groups (Figure 1a), NEURL1 gene expression was significantly decreased in the HFA group (p=0.006). However, no significant differences were detected between ASD and other groups in the NEURL1 gene expressions. The p value between the ASD and HFA groups was 0.526 (p>0.05), whereas the p value between the ASD and the control groups was 0.85. No significant differences were detected between the groups in the RGS14 gene expressions (Figure 1b): the p value between ASD and HFA was 0.077, the p value between ASD and control groups was 0.219, whereas the p-value between the HFA and control groups was 0.790.

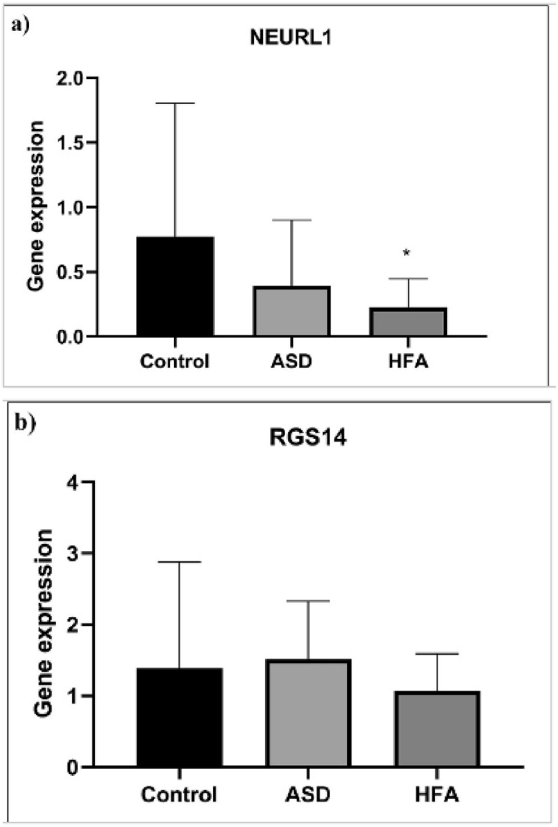

Fig. 1 Real-time RT-PCR results of putative genes associated with learning and memory. The data are given as means±SD *p<0.05 vs. control. a) NEURL1 gene expression comparison between groups. b) RGS14 gene expression comparison between groups.

In addition, the relationship between the NEURL1 and RGS14 genes was evaluated among the patient groups. In the ASD group, the Spearman correlation coefficients between NEURL1 and RGS14 expression levels were found to be 0.65 (p=0.008). However, it was found to be 0.344 (p=0.274) in the HFA group. A strong positive correlation was observed between the NEURL1 and RGS14 genes in the ASD group. When the gene expressions were compared with demographic features, we found a negative correlation between the learning and memory problems and RGS14 gene expression (Table 3).

Discussion

ASD is a complex neurodevelopmental disease. With ASD patients, there are disorders in cognitive episodic memory, future planning and learning difficulties [7, 8, 21]. Molecular and genetic studies suggest that the pathologic changes involved in ASD are likely to alter synapse formation and function, therefore affecting hippocampal-based learning and memory [7, 22]. Overexpression of

Table-3. Correlations of gene expressions and demographical findings.

	Genes	NEURL1	RGS14	Age	ID	NDR	Cons.	Learning and Memory Dif.
ASD	NEURL1							
	Spearman Correlation	-	0,594*	0,014	0,098	-0,077	0,136	0,174
	Sig. (2-tailed)	-	0,032	0,959	0,364	0,392	0,314	0,268
	RGS14							
	Spearman Correlation	0,594*	-	-0,243	0,377	-0,031	0,192	0,318
	Sig. (2-tailed)	0,032	-	0,382	0,083	0,456	0,246	0,124
HFA	NEURL1							
	Spearman Correlation	-	-0,344	0,087	-	-0,097	-	0,231
	Sig. (2-tailed)	-	0,274	0,788	-	0,382	-	0,235
	RGS14							
	Spearman Correlation	-0,344	-	0,384	-	-0,107	-	-0,471*
	Sig. (2-tailed)	0,274	-	0,175	-	0,357	-	0,045

Statistically significant correlations are shaded. *Correlation is significant at the 0.05 level (2-tailed). NDR: Neurological Disease in Relatives, Cons: Consanguinity, Learning and Memory Dif: Learning and Memory Difficulties.

the NEURL1 gene and its related mechanisms have been shown to be effective in learning and memory in animal ASD models [11, 12, 14, 17]. In addition, the RGS14 gene has been shown to be a natural suppressor of synaptic plasticity, memory and hippocampal-based learning [18, 19, 23]. However, the effectiveness of these genes on learning and memory is not yet clear and has not been studied before in patients with ASD. In our study, we investigated the differences in mRNA expression levels of NEURL1 and RGS14 genes in blood samples of ASD and HFA patients and control groups, and we evaluated the role of these genes in the pathogenesis of ASD in terms of its effects on learning and memory problems.

Several studies have shown that the NEURL1 gene suppresses the CPEB3 and, accordingly, increases synaptic plasticity and enhanced hippocampal-based learning and memory as well [14, 16]. Vogler et al. showed that human CPEB3 (activated by monoubiquitination NEURL1) plays a role in human episodic memory [24]. Pavlopolus et al. (2008) showed that overexpression of NEURL1 in the peripheral neurons of the adult Drosophila results in a dosage-dependent enhancement of long-term memory (LTM) [25]. Pavlopolus et al. (2011) showed that the number of synapses and synaptic plasticity increased in the hippocampus as a result of over-expression of NEURL1 in mice with ASD, and stated that this gene is also effective in learning and memory in mammals [14]. Studies on humans about this subject are very limited, therefore it is imperative that this gene be studied in patient groups following animal experiments. Our results are consistent with earlier studies in models of ASD. According to the results of our study, NEURL1 gene expression was decreased in both patient groups compared to the control. However, when evaluated clinically, NEURL1 gene expression did not correlate with ID, learning and memory, therefore we suggest repeating this relationship examination with a larger number of patients. Although this study will guide further research, we suspect that gene expressions in peripheral blood may be inaccurate, therefore studying NEURL1 gene expression from human brain tissues may be a more preferable option.

Despite the fact that RGS14 plays a basic immunological role in tissues like the spleen, thymus and lymphocytes, it is one of the negative regulator genes of the hippocampal-based learning and memory in the brain [19, 23]. Studies in this area mostly focus on experimental mouse models. For instance, it was observed that the cells of the RGS14 gene knockout (RGS14-KO) mice, obtained from the hippocampus CA2 region, respond to various electrochemical stimuli faster, making neuronal connections stronger and forming more complex synapses [19]. Lee et al. showed that RGS14 knockout mice showed a manifest increase in spatial learning and object recognition memory compared to wild-type mice, but that there was no difference in their performance in non-hippocampal behaviour tests.

This gene is therefore predicted to be effective in hippocampus-mediated learning and memory [18]. In our study, mRNA expression levels of the RGS14 gene were evaluated in ASD and HFA patients. No significant differences were detected between groups in the RGS14 gene expressions, although there was a negative correlation between learning and memory difficulties and the RGS14 gene in HFA patients. We believe meaningful data can be obtained with additional patients and more comprehensive studies on this subject. In addition, in order to establish a clear relationship with autism, it is recommended these results be supported by studies using brain tissue in experimental models.

Conclusion

In the present study, we examined the relationship of the NEURL1 and RGS14 genes expressed in the hippocampus, with learning and memory disorders in ASD and HFA patients. We showed that the NEURL1 gene may affect learning and memory in ASD. Moreover, it has also been shown that the RGS14 gene has a relationship with the clinical features of ASD, however, aside from this, we suspect that gene expressions will yield clinically significant results in studies with additional patients and brain tissue analyses. This study was the first to examine the NEURL1 and RGS14 genes in patients with ASD and in this respect, we expect it will make important contributions to the literature.

Conflict of Interest: The authors declare no conflict of interest related to this article.

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