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Expression Profiles Of PTEN And POGZ Genes In Patients With Autism

Otizmli Hastalarda PTEN Ve POGZ Genlerinin Ekspresyon Profilleri

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ABSTRACT

Aim: Autism spectrum disorder (ASD), a group of heterogeneous neurodevelopmental disorders, is characterized by complex behavioral phenotypes. Despite extensive studies over many years, the causes of ASD are still unknown. PTEN and POGZ genes are studied as candidate genes that may be responsible for the ASD phenotype. We aimed to investigate the expression levels of PTEN and POGZ genes in autistic patients.
Methods: Gene expressions of PTEN and POGZ were investigated in 50 ASD patients and 50 age and gender matched healthy controls. This study was conducted in the Erciyes University Genome and Stem Cell Center (GENKOK).
Results: POGZ gene expression was increased in patients compared to controls. According to gender, the expression results of the autistic male patients were significant. PTEN mRNA expression was not statistically significant but found to be lower in patients than in controls. The relationship between the expression of these genes and cognitive deficits was not significant.
Conclusion: We recommend investigating other possible candidate genes in larger cohorts and comparing the results with different additional cilinical findings in ASD.

Key Words: Autism, Autism Spectrum Disorders, PTEN, POGZ, Expression

ÖZ

Amaç: Otizm spektrum bozukluğu (OSB), karmaşık davranışsal fenotiplerle karakterize, heterojen bir grup nörogelişimsel bozukluktur. Uzun yıllar boyunca yapılan kapsamlı çalışmalara rağmen, OSB'nin nedenleri hala bilinmemektedir. PTEN ve POGZ genleri, OSB fenotipinden sorumlu olabilecek aday genler olarak gösterilmiştir. Otistik hastalarda PTEN ve POGZ genlerinin ekspresyon düzeylerini araştırmayı amaçladık.
Yöntem: OSB tanılı 50 hastada ve yaş-cinsiyet uyumlu 50 sağlıklı kontrolde PTEN ve POGZ gen ekspresyonları araştırıldı. Bu çalışma Erciyes Üniversitesi Genom ve Kök Hücre Merkezi'nde (GENKÖK) yapılmıştır.
Bulgular: POGZ geninin hastalarda kontrollere göre daha fazla eksprese olduğu ve otistik erkek hastalarda bu genin ekspresyonunun anlamlı olduğu bulundu. PTEN gen ekspresyonu istatistiksel olarak anlamlı değildi ancak hastalarda kontrollere göre daha düşük bulundu. Bu genlerin ekspresyonu ile bilişsel gerilik arasındaki ilişki ise anlamlı değildi.
Sonuç: Daha büyük hasta grupları ile diğer olası aday genlerin araştırılmasını ve sonuçların farklı ek klinik belirtilerle hastalarda karşılaştırılmasını önermekteyiz.

Anahtar Kelimeler: Otizm, Otizm Spektrum Bozuklukları, PTEN, POGZ, Ekspresyon

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by repetitive and restricted behaviors and interests, as well as social communication impairments [1-3]. Autism is a common subtype of ASD [4]. It is a chronic disease that starts in early childhood and lasts for life. There has been a significant increase in the autism incidence worldwide: according to recent reports, 1 in every 54 children has the condition [5]. The complex etiology of the disease causes different phenotypes to occur, even in the same family. Despite extensive studies over many years, the causes of ASD are still unknown. It is known that it is not a single gene which is responsible for the pathogenesis of ASD [6-12]. To date, more than 800 ASD candidate genes have been identified and they are involved in various biological pathways [13].

Both of PTEN and POGZ genes are shown as candidate genes that may be responsible for the ASD phenotype [13]. PTEN is a gene on chromosome 10 and it has an epigenetically different function: its gene function is namely important in neurodevelopment [14]. Deletion of the PTEN gene results in death during the embryonic period [15]. It may contribute to the diversity of the ASD phenotype as an important regulator of the PI3K/AKT mTOR pathway [15,16]. Several roles of the PTEN gene in autism have been shown in various studies [17-19].

POGZ is a gene that encodes pogo transposable element-derived protein with zinc finger domain affecting ASD [20]. POGZ has a major role in chromatin regulation, cellular function and gene expression. Disorders in chromatin-related mechanisms may cause pathological effects [21]. POGZ is highly expressed in the human fetal brain [21,22]. POGZ deficiency may affect mitosis, brain development and dysfunction [23]. A recent study demonstrated that Pogz deficient mice had been mimicking several of the ASD symptoms including learning and motor deficits, growth impairment, microcephaly and increased sociability [24].

Studies have shown that there is a relationship between PTEN and POGZ genes and ID accompanying some autism cases. Thus we used these genes, which are more associated with clinical findings of autism [15,17-19,25-27]. This is the first report investigating the expression of target genes (PTEN, POGZ) in 50 ASD patients and 50 age-gender matched healthy controls in Turkey. We also investigated whether these gene expressions were related to cognitive impairment in ASD patients.

MATERIAL AND METHODS

Ethical Compliance

This study was approved by the institutional ethical board of Erciyes University (No:2016/491). Informed consents were obtained from the parents of the children who participated in the study.

Selection of patients

Fifty patients aged 2 to 10 were enrolled from Erciyes University Faculty of Medicine Department of Child Psychiatry, after undergoing psychiatric, physical and neurologic examinations. All children with ASD were newly diagnosed by a childhood and adolescence psychiatrist, based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V). The Childhood Autism Rating Scale (CARS) scale was used to assess the severity of ASD from mild to moderate to severe [28]. Fifty healthy controls aged 1 to 10 without a chronic, medical and psychiatric medication or genetic disease, were included in the study. Whole blood samples of patients and healthy controls were taken into sterile 2 ml vacuum tubes containing EDTA (ethylenediamine-tetraacetic acid) for further analysis. All of the blood samples from patients were taken before starting the medications to avoid the possible effects for gene expression.

RNA isolation and gene expression studies

We performed the analysis in the Erciyes University Genome and Stem Cell Center (GENKOK). Total RNA was isolated from peripheral blood samples (TRIzol, Roche, Germany). The RNA quality and quantity were measured with BioSpec-Nano Spectrometer. Complementary DNA (cDNA) was synthesized from the RNA obtained using the Transcriptor High Fidelity cDNA synthesis kit (Roche, Germany). Expressions of POGZ and PTEN genes were investigated with Quantitave Real-Time PCR (LightCycler 480, Roche,

Germany) using SYBR green. The experiment comprised the steps of the reaction mixture for 1 cycle of 10 min at 95˚C for deactivation and subsequently, 45 cycles of 10 sec each at 95˚C, 30 sec at 60˚C, 1 sec at 72˚C for denaturation and 30 sec at 40˚C for cooling. Each sample was double studied and beta-actin (ACTB) was selected as housekeeping gene. Results of the target gene expression levels were determined by delta Ct method.

Statistical analysis

The statistical results of this study were calculated using GraphPad Prism (Version 6.01) program and the graphs of the results were prepared again with this program. Comparisons between the groups were evaluated by nonparametric t-test. $p<0.05$ was considered significant.

RESULTS

Study groups

The study group consisted of 50 individuals with 39 males and 11 females with the age range of 2 to 10 years, whereas the control group consisted of 39 males and 11 females, with the age range of 1 to 10 years. The characteristics of the patients included in the study are shown in Table 1. Seven of the patients identified for this study had consanguineous marriage, 23 had congenital anomalies and 19 had an intellectual disability (ID). Table 2 shows the patients with ASD included in the study and their clinical findings.

Table 1. Demographics of patients and controls included in the study

Demography	Autism (n=50)	Control (n=50)
Gender	39 Males and 11 Females	39 Males and 11 Females
Average of age	4.08	3.85
Range of age	2-10	1-10

Gene expression results of POGZ and PTEN genes in patients with ASD and controls

The expression levels of POGZ and PTEN genes in the blood of autistic patients were determined. The expression results of POGZ gene was statistically significant ($p< 0.0001$), although those for the PTEN gene was not significant ($p=0.7884$). Figure 1 shows gene expression profiles of the groups. Figure 1A depicts the comparison of expression of POGZ and PTEN genes in 50 ASD patients and 50 controls. While the POGZ gene was expressed more in patients with autism than controls, the PTEN gene was found to be less expressed in patients with ASD than in the controls.

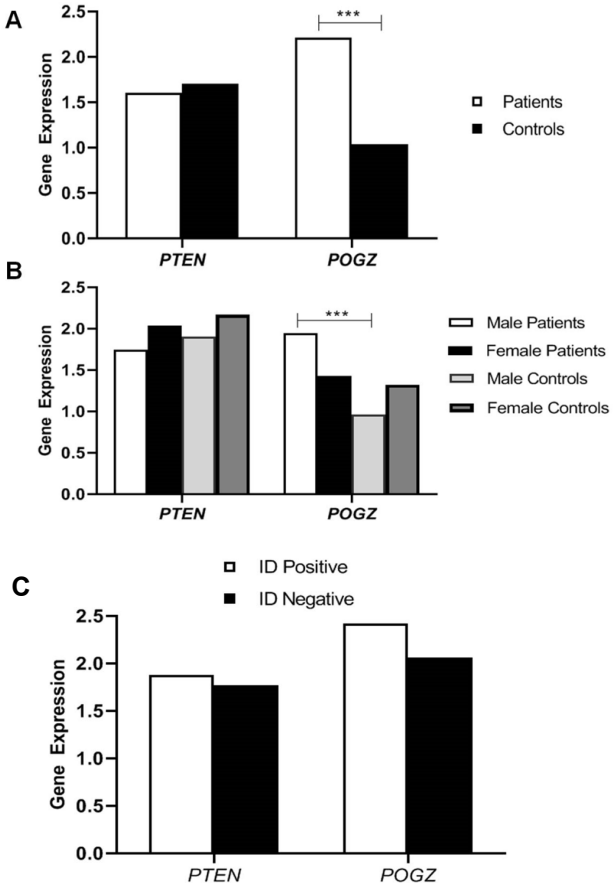

Figure 1. Gene expression profiles of the groups. (A) Expression profiles of PTEN and POGZ genes in 50 ASD patients and 50 controls. (B) Expressions of PTEN and POGZ genes according to gender. (C) The comparison of expressions of PTEN and POGZ genes with ID Positive and ID Negative patients

When compared according to gender, the expressions results of these genes were not statistically significant in male and female patients (for POGZ $p=0.2380$, for PTEN $p=0.6556$, respectively) (Figure 1B). While the expression of POGZ gene was statistically significant by comparing male patients and male controls ($p<0.0001$), PTEN gene expression was not significant in male patients and male controls ($p=0.7513$). The expression results of genes were not statistically significant in female patients and female controls (for POGZ $p=0.8236$, for PTEN $p=0.8862$, respectively).

It was also investigated whether the expression

Table 2. Clinical findings in patients with autism

No	Disease Group	Gender (Male, Female)	Age (Year)	Consanguinity	Congenital Anomaly	Intellectual Disability
1	ASD	M	2	Negative	Negative	Negative
2	ASD	M	6	Negative	Positive	Positive
3	ASD	M	3	Negative	Positive	Negative
4	ASD	F	3	Negative	Positive	Positive
5	ASD	M	6	Positive	Positive	Negative
6	ASD	M	6	Negative	Negative	Negative
7	ASD	M	5	Negative	Negative	Negative
8	ASD	M	4	Negative	Negative	Negative
9	ASD	M	6	Negative	Positive	Positive
10	ASD	F	4	Positive	Positive	Positive
11	ASD	M	4	Positive	Negative	Positive
12	ASD	M	3	Negative	Positive	Negative
13	ASD	M	3	Negative	Negative	Positive
14	ASD	M	3	Negative	Negative	Negative
15	ASD	F	3	Negative	Negative	Negative
16	ASD	M	9	Negative	Negative	Negative
17	ASD	F	9	Negative	Negative	Negative
18	ASD	F	4	Negative	Negative	Negative
19	ASD	M	9	Positive	Negative	Negative
20	ASD	M	4	Negative	Positive	Positive
21	ASD	M	4	Negative	Positive	Negative
22	ASD	M	2	Negative	Positive	Negative
23	ASD	M	2	Negative	Positive	Negative
24	ASD	M	4	Negative	Negative	Positive
25	ASD	M	5	Negative	Negative	Positive
26	ASD	F	3	Negative	Negative	Negative
27	ASD	M	4	Negative	Positive	Negative
28	ASD	M	3	Negative	Negative	Positive
29	ASD	M	3	Negative	Negative	Positive
30	ASD	M	2	Negative	Negative	Positive
31	ASD	F	3	Negative	Negative	Negative
32	ASD	M	4	Positive	Positive	Negative
33	ASD	M	5	Negative	Positive	Negative
34	ASD	M	3	Negative	Positive	Negative
35	ASD	M	4	Negative	Positive	Negative
36	ASD	M	5	Negative	Positive	Negative
37	ASD	F	3	Negative	Positive	Negative
38	ASD	M	3	Negative	Negative	Negative
39	ASD	M	3	Negative	Negative	Negative
40	ASD	M	4	Negative	Negative	Positive
41	ASD	F	3	Negative	Negative	Positive
42	ASD	F	4	Positive	Negative	Positive
43	ASD	M	4	Negative	Positive	Positive
44	ASD	M	3	Negative	Positive	Positive
45	ASD	M	3	Negative	Positive	Negative
46	ASD	M	4	Negative	Positive	Negative
47	ASD	M	2	Negative	Negative	Negative
48	ASD	F	4	Negative	Negative	Positive
49	ASD	F	9	Negative	Negative	Positive
50	ASD	M	3	Positive	Positive	Negative

levels of PTEN and POGZ genes are associated with the finding of ID and this finding was shown in Figure 1C. There were no significant differences for PTEN and POGZ gene expressions with/without ID (p=0.8519; p=0.5063).

DISCUSSION

Genetics plays a key role in the etiology of ASD [8,29]. PTEN and POGZ genes are shown as candidate genes that may be responsible for the ASD phenotype [13]. Since the role of these genes in autism is not well known, the expressions of PTEN and POGZ genes were investigated in this study, through the blood samples of Turkish patients with autism and corresponding controls.

The PTEN gene can contribute to the diversity of the ASD phenotype as an important regulator of the PI3K/AKT/mTOR pathway [15]. This signaling pathway activity is required for cell growth, survival and proliferation. Therefore, abnormalities in this pathway cause psychiatric and neurological disorders such as schizophrenia, autism and brain tumors [19]. A study with Pten knock-out mice was reported to result in long-term changes in autistic-like behavior (social behavior, repetitive behavior and anxiety, memory and learning deficits) [15]. The most common clinical finding in humans with mutated PTEN is macrocephaly [14,30]. Butler et al. investigated the PTEN gene mutation in 18 patients (13 males and 5 females aged 3-18 years) who were diagnosed with ASD and macrocephaly. As a result of the study, it was determined that three male patients were carriers of germline PTEN mutation [27]. Kaymakcalan et al. also identified three pathogenic/likely pathogenic mutations by PTEN gene sequence analyses in Turkish ASD and macrocephaly children [31].

Some of the PTEN and POGZ mutations have been related to ASD [15,21,27]. PTEN mutation carriers are strongly affected by genetic and environmental factors. Individual mutations lead to very different phenotypes, even within the same family [32,33]. Recent case reports have suggested that 25% to 50% of ASD children with PTEN mutations were identified [33,34]. Individuals with autism who have mutations in the PTEN gene have a distinct profile of cognitive impairments and structural abnormalities in the brain [35-37]. In our study, it was found that there was less PTEN gene expression in the patient group as opposed to the controls, however this finding was statistically insignificant (p=0.7884). Expression changes of this gene were also

investigated on gender basis and it was found that there was a decrease in PTEN expression of autistic male patients, compared to the controls. In female patients, PTEN was found to be less expressed than in the controls. Research on both the number of patients and the basis of gender may provide more detailed information about how this decrease in PTEN expression is reflected in the etiology of autism.

POGZ encodes pogo transposable element-derived protein with zinc finger domain affecting ASD [20]. Previous studies have shown that POGZ is involved in chromatin remodeling, neurite outgrowth, neuronal proliferation and gene transcription regulation [21,38-40]. In fetal brain tissues, the POGZ expression pattern may well play an essential role in early embryonic development [26]. POGZ deficiency may affect mitosis, brain development and dysfunction [23]. A recent study demonstrated that Pogz deficient mouse mimicked several of the ASD symptoms, including learning and motor deficits, growth impairment, microcephaly and increased sociability [24].

Pathogenic POGZ mutation causes impaired cortical development and reversible autism-like phenotypes. De novo mutations were likely gene-disrupting variants that cause ID and ASD [25]. Matsumura et al. showed that POGZ regulates neuronal development, and POGZ de novo mutations impaired neuronal development in the developing mouse brain and induced pluripotent cell lines from an ASD patient [41]. Our expression results of POGZ gene was statistically significant. POGZ gene was expressed more in patients with autism. Also we were investigated expression changes of the POGZ gene in terms of gender. Autistic males had more POGZ expression than the controls and this result was found to be significant. In female patients, POGZ was found to be more expressive than the controls but this finding was not significant. With the small number of female patients included in this study, the increase in gene expression may not be found to be significant. Genotype–phenotype correlation analysis has revealed that there is a relationship between and PTEN and POGZ genes with ID accompanying some autism cases [15,26]. In our study, POGZ and PTEN expressions were examined in terms of ID associated with autism. The results of both genes were not statistically significant.

CONCLUSION

In future studies, by investigating the expression of PTEN and POGZ genes in larger cohorts and comparing the obtained results with the other clinical findings determined in Turkish ASD patients, the unknowns regarding these genes in the etiology of autism can be eliminated. They may be used as a potential biomarker in the clinic and may contribute to the development of clinical phenotype-specific treatment options among patients. It will also be useful to investigate and find other genes, which may be new candidate genes for autism. We only used blood samples from the patients because the difficulty and inaccessibility in taking and analyzing brain tissue, and this remains one of the biggest obstacles in autism neuropathology [42]. Also, the expression of the genes may be studied in specific brain regions and other biological samples from autism patients. Therefore, the real effect of the expression of these genes on the autism phenotype may be determined by further analysis.

Conflict of Interest: The author declares no conflict of interest related to this article.

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Ethics Committee Approval: The study was approved by the Ethical Board of Erciyes University (No. 2016/491) and conducted in accordance with the Declaration of Helsinki and local laws, which afforded greater protection to the participants.

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