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Relation of *ATPase6* Mutations and Telomere Length in Schizophrenia Patients

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Objective: Schizophrenia is a serious mental disorder. Mutations in mitochondrial genes can change energy metabolism. Telomere is a tandem sequence at the end of chromosomes. Shorter telomere length has been shown in schizophrenia. The aim of this study was to determine the relationship between *ATPase6* gene mutations and telomere length in schizophrenia patients.
Methods: Blood samples of 34 patients and 34 healthy controls were used. In this study conventional PCR, Sanger sequencing technic and real-time PCR were utilized.
Results: Five different mutations (A8860G, A8836, G8697A, C8676T, and A8701G) in the *ATPase6* gene were identified in schizophrenia patients. The most seen mutation was A8860G (94%). Telomere length analysis indicated the relation of *ATPase6* gene mutations and telomere length variations (p = 0.001). Patients carrying the A8860G mutation had shorter telomere lengths than patients carrying other mutations. Comparing telomere length between schizophrenia patients and healthy controls revealed that the mean telomere length of schizophrenia patients was shorter than healthy controls (p = 0.006). The demographic analysis demonstrated a significant relationship between marital status and telomere length (p = 0.011). Besides that, the duration of the illness is another factor that impacts telomere length (p = 0.044). There is no significant relation between telomere length and other clinical and demographic characteristics including education status, age, gender, etc.
Conclusion: In conclusion, telomere length and *ATPase6* gene mutations have a significant relation. Studies with larger patient populations and investigation of other mitochondrial gene mutations will make the clearer link between telomere length and mitochondrial mutations.

KEY WORDS: ATPase6; Mitochondria; Schizophrenia; Telomere.

INTRODUCTION

Schizophrenia is a mental disorder characterized by some serious symptoms, including hallucination, delusions, disorganized speech, cognitive dysfunction, and lack of motivation. Besides the hereditary factors, environmental factors like fetal infection, alcohol use, environmental toxins, drug addiction, maternal malnutrition may cause the development of schizophrenia [1,2]. Each symptom is crucial to single out schizophrenia from other mental disorders. Recent studies have shown that impairment of brain development and neuronal connection may be related to the pathology of schizophrenia [3].

Mitochondria is a crucial organelle for a cell because of its role in cell death. Besides that, mitochondria affect neural activity, synapse function, and morphogenesis [4]. Mitochondrial dysfunction causes impairment of the energy state of cells, which may, in turn, give rise to alterations of myelination, neuronal development, and neural connections [3]. Several studies have suggested a relationship between mitochondrial dysfunction and the increasing risk of schizophrenia [3]. There is a general understanding that adenosine triphosphate (ATP) synthase is

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an important enzyme for the process of energy production in the cell [5]. In the previous studies, *ATPase6* gene encoded in mtDNA were shown to have mutations in different diseases [6]. Transcriptomic, proteomic, and metabolic studies using brain tissues revealed that genes associated with energy metabolism and oxidative stress involved in reactive oxygen species (ROS) showed that 90% differences [7] related to impairment, mitochondrial hypoplasia, and alteration of mitochondrial gene expressions [8,9] in schizophrenia patients when compared with the control group [7]. Alterations of mitochondrial function lead to an increase in ROS levels [10]. Increased ROS levels cause damage to DNA, including telomere regions [11]. Because of having a guanine-rich region, telomere tends to break DNA because of oxidative stress [12].

Telomere is a tandem sequence at the end of mammals' chromosomes and protects genes from degradation and recombination [13]. In each cell division, the telomere diminishes and when arriving at a critical point of proliferation it is arrested and apoptosis tendency increases [14]. Telomere shortening and decrease in telomerase activity, which were shown in previous studies in chronic stress patients [15], were also shown in patients with mental illness [16] and patients with schizophrenia [17]. Otherwise, smoking [18], aging, stress [15] have been associated with telomere shortening.

Though studies have been expanding, yet there are no approved molecular markers for diagnosing schizophrenia, accurately. Although there is an increasing number of studies investigating schizophrenia, no study has evaluated the association between *ATPase6* mutations and telomere length in schizophrenia patients. In this study, we have investigated the potential link between telomere length, *ATPase6* mutations, and clinical parameters in schizophrenia patients and the control group.

METHODS

Participants

We recruited 34 healthy volunteers with no psychiatric disorder and 34 patients who had been diagnosed with schizophrenia at Ataturk University Research Hospital Psychiatric Clinic between 2020 and 2021. The range of age of schizophrenia patients and healthy volunteers was 18−70. Participants with other chronic medical conditions (including psychiatric comorbidities and diseases as hypertension, cancer, diabetes, etc.) were excluded because their presence in the study could have led to differences in biological parameters that were being explored. Substance use was excluded. The present study was approved by the local Ethic Committee of Ataturk University School of Medicine (decision no: 55). Patients and/or their relatives and healthy subjects were educated about the aim of this study, and written informed consent was obtained from all the participants. For diagnosis Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) [19], was used by an experienced psychiatrist who worked for this study.

DNA Extraction

DNA isolation were performed of 200 µl peripheral blood using DNeasy Blood & Tissue Kit (Qaigen, Hilsen, Germany) according to manufacturer's protocol. Genomic DNA concentration was measured at A260/280 ratio via Epoch Spectrophotometer System and Take3 Plate (BioTek, Winooski, VT, USA) then samples were stored at −20°C until polymerase chain reaction (PCR) analysis.

PCR and Sanger Sequencing

Genomic DNA was amplified with *ATPase6* primer pair and Ecotaq master mix (Eco-Tech Biotechnology, Erzurum, Turkey). Agarose gel electrophoresis was utilized to determine the 675-bp amplicon of *ATPase6* gene. To 25-µl reaction mix, 10-pmol/µl primer and 100-ng/µl gDNA were added. PCR program used in SensoQuest (Labcycler, Göttingen, Germany) was at 94°C for 5 minutes, at 94°C for 1 minute, at 59°C for 1 minute, at 72°C for 1 minute, and at 72°C for 5 minutes and had 35 cycles. Amplified PCR products were used to identify DNA sequence variants via Sanger DNA sequencing. To analyze DNA sequence variants Chromas Lite software and other bioinformatics software were used. Variants were searched on an online website (http://www.mitomap.org/MITOMAP).

Telomere Length Analysis

Quantative real-time polymerase chain reaction (QRT-PCR) was used in order to determine telomere length via SsoAdvanced Universal Green Supermix (Bio-Rad, Hercules, CA, USA) according to the manufacturer's protocol. PCR reaction consists of a 10 µl master mix, a 250 nM primer, and a 10 ng gDNA. PCR program used in Bio-Rad CFX96 (Bio-Rad) was at 98°C for 2 minutes, at

95°C for 15 seconds, and at 60°C for 30 seconds. 36B4 gene was used as an internal control. All reactions were duplicated. Telomere and 36B4 primer sequences had been published before [20]. The length of telomere was calculated with $2^{-\Delta\Delta Ct}$ method.

Psychiatric Evaluation

For diagnosis, DSM-V [19] was used by an experienced psychiatrist who was involved in this study. Positive and Negative Syndrome Scale (PANSS) [21] is a semi-structured rating scale that consists of thirty items with a seven-point severity range, and it is widely used to assess severity of schizophrenia. Clinical global impressions (CGI) [22] consist of positive, negative, depressive, and cognitive functions used to evaluate the severity of the disease [23]. The Brief Psychiatric Rating Scale (BPRS) is widely used for getting quick evaluation of patients' conditions during interview for determining the presence and degree of severity of the symptoms in each item [24].

Statistically Analysis

According to the results relation of *ATPAase6* gene mutations and telomere length was evaluated statistically. In order to analyze data about *ATPase6* gene mutations and telomere length by parametric and nonparametric tests Graphpad Prism 7.04 was utilized. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to test whether participants' telomere length was normally distributed. Telomere length of patients was evaluated by one-way ANOVA according to mutations type. Relation between clinical parameters and telomere length was analyzed with Kruskal–Wallis and Mann–Whitney *U* test. Telomere length differences between patients and healthy control were analyzed with the Mann–Whitney *U* test. We estimated the sample according to clinical settings and the will to participate in the study and also we paid attention to take enough participants to make parametric tests in statistical analysis. Results with $p < 0.05$ value were considered as significant.

RESULTS

Characteristics of Participants

Some demographic information and clinical characteristics of patients have been summarized in Table 1. Mean of patients age was 37 ± 10 (mean ± standard deviation; females 38 ± 10, males 35 ± 12) and age of onset was 29 ± 9. Education status of patients was mainly elementary school degree. Tobacco was used by 38% patients. Alcohol consumption was 3% among patients. Among the patients, the rate of those who have children, have suffered from this disease for more than five years, are married, and have a close relative with a psychiatric disease is 29%. There were 35% patients who had underwent treatment for schizophrenia longer than five years. Mainly three antipsychotics were used among the patients. Percentage of the patients who used aripiprazole was 44%, who used clozapine was 18%, and who used Paliperidone was 26%. Some patients' information was not accessible.

Table 1. Characteristics of the patients

Parameters	Patients, n (%)
Sex	
Female	16 (47)
Male	18 (53)
Education status	
Elementary and high school	21 (62)
University or higher	6 (18)
Unidentified	7 (20)
Using tobacco	
Yes	13 (38)
No	15 (44)
Unidentified	6 (18)
Having children	
Yes	10 (29)
No	18 (53)
Unidentified	6 (18)
Marital status	
Married	10 (29)
Single	19 (56)
Unidentified	5 (15)
Presence of psychiatric disease in relative	
Yes	10 (29)
No	18 (53)
Unidentified	6 (18)
Duration of illness (yr)	
≤ 5	22 (65)
> 5	10 (29)
Unidentified	2 (6)
Antipsychotic medication	
Aripiprazole	15 (44)
Clozapine	6 (18)
Paliperidone	9 (26)
Unidentified	4 (12)
Duration of treatment	
≤ 5	16 (47)
> 5	12 (35)
Unidentified	6 (18)

Clinical Assessment

All patients were evaluated by clinical assessment tools, such as PANSS [21], CGI [22], and BPRS [24] before and after treatment to evaluate treatment efficiency. Pretreatment and post-treatment of PANSS ($p < 0.0001$) and BPRS ($p < 0.0001$) scores were evaluated and were significantly different, but CGI score was not significant. Pretreatment PANSS score was 91.65 ± 16.49 (mean ± standard deviation), meaning high grade of severity and post-treatment was 61.57 ± 14.04. Pretreatment CGI score was 5.565 ± 0.84 and post-treatment CGI score was 5.391 ± 1.9. While BPRS pretreatment score was 43.52 ± 10.76 and then it decreased to 22.24 ± 9.2 after treatment. Relation between telomere length and PANSS, CGI, and BPRS scores was evaluated, but any correlation between telomere length and severity of disease was not found. Relation between mutations and severity of disease was also analyzed. No mutation type was significantly associated with PANSS, CGI, or BPRS scores ($p > 0.05$).

ATPase6 Mutations in Schizophrenia Patients

To *ATPase6* gene, 675 bp amplicon was detected by agarose gel electrophoresis for all patients (Fig. 1). *ATPase6* gene mutations of schizophrenia patients were summarized in Table 2. *ATPase6* gene of 34 schizophrenia patients was analyzed. In 34 patients' samples, 5 different mutations (A8860G, A8836, G8697A, C8676T, and A8701G) were detected. *ATPase6* mutations were determined in all patients however, the A8860G mutation was the most seen one (94%). In just 3 patients (9%) had two mutations. We analyzed the association of mutations type and patients' characteristics and found no significant relation ($p > 0.05$).

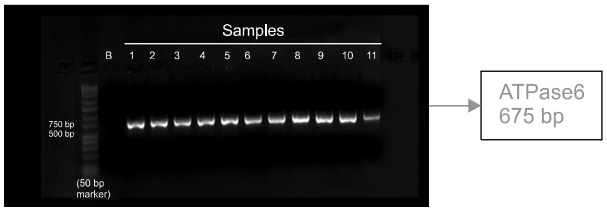

Fig. 1. Agarose gel electrophoresis showing ATPase6 gene PCR products (675 bp) of schizophrenia patients. DNA ladder 50 bp; B, blank not including DNA sample.
PCR, polymerase chain reaction.

Table 2. *ATPase6* mutations frequencies in schizophrenia patients

Nucleotide	Codon	Number
A8860G	T112A	32
A8836G	M104V	1
G8697A	M57M	1
C8676T	I50I	1
A8701G	T59A	1
The total number of mutations identified		36
The total number of the patients carrying the mutation		34
The number of sample examined		34

Telomere Length of Schizophrenia Patients and Control Group

In the study telomere length of 34 patients and 34 healthy participants were amplified using 36B4 as an internal control. Length of telomere in patients (1.34818 ± 1.329) (mean ± standard deviation) was shorter than healthy control (2.41258 ± 1,395) ($p = 0.006$) (Fig. 2).

In Table 3 telomere length of schizophrenia patients and its relation to demographic information were mentioned. We grouped patients like in Table 3 according to their $2^{-\Delta\Delta Ct}$ value of telomere length analysis. Assessment of telomere length of men and women showed that women had longer telomere but it is not significant ($p > 0.05$). Old age is an important factor for telomere length. Comparing men and women younger than 33 years old showed that the telomere of women was longer than those of men ($p = 0.047$) (data not shown in Table 3). While we were evaluating the education status and telomere length, we separated all patients into two groups as in Table 3. Patients certificated with elementary or high school degrees had longer telomere than patients certificated with university

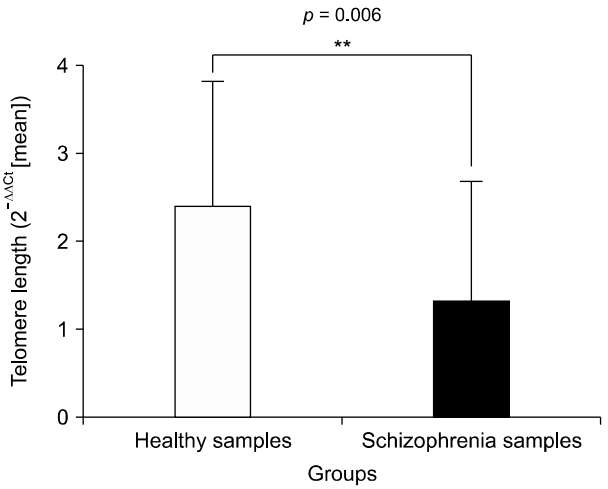

Fig. 2. Telomere length in patients compared with healthy controls.
**Means statically very significant.

Table 3. Telomer length and characteristics of the patients

Parameters	Telomer length	p value
Age (yr)		0.4603
> 33	2.33454	
≤ 33	1.34755	
Sex		0.2361
Female	2.72213	
Male	1.48866	
Education status		0.1171
Elementary and high school	1.94817	
University or higher	0.796679	
Using tobacco		0.1148
Yes	1.35879	
No	2.24947	
Having children		0.0527
No	1.38581	
Yes	2.49534	
Marital status		0.0110*
Single	1.25318	
Married	2.66945	
Presence of psychiatric disease in relative		0.8868
Yes	2.06568	
No	1.585	
Duration of illness (yr)		0.0444*
≤ 5	0.977123	
> 5	2.16536	
Antipsychotic medication		0.2736
Aripiprazole	2.33094	
Clozapine	1.45167	
Paliperidone	0.853389	
Duration of treatment		0.8695
≤ 5	1.65119	
> 5	1.87161	

Values ($2^{-\Delta\Delta Ct}$) are presented as the mean of telomere length.
*$p < 0.05$ was considered significant statistically.

or higher degrees but it is not significant ($p > 0.05$). Using tobacco had not significant effects on telomere length in our patients however smoking patients had shorter telomere length ($p > 0.05$). Patients who suffered from schizophrenia for more than 5 years had longer telomere (p = 0.044) (Fig. 3A). Having children had a positive effect on the telomere length of patients but it is not significant. Marriage also had positive effects on telomere length, married patients had longer telomere than single patients (p = 0.011) (Fig. 3B). The presence of psychiatric disease in relative was 29% and 60% of them was first-degree relative but it did not affect telomere length. Patients treated

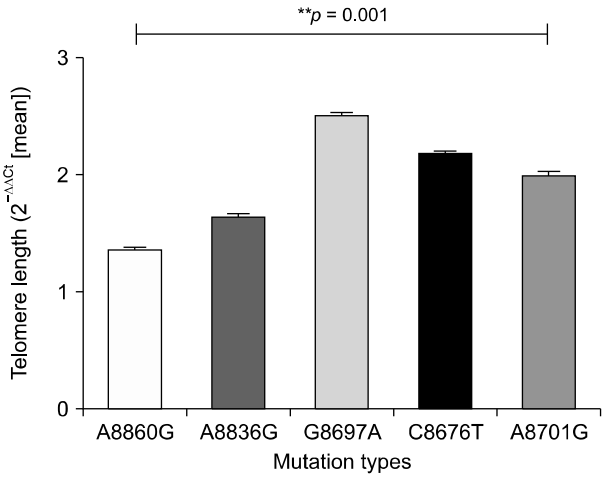

Fig. 4. Relation of telomere length and *ATPase6* gene mutations in schizophrenia patients.
**Means statically very significant.

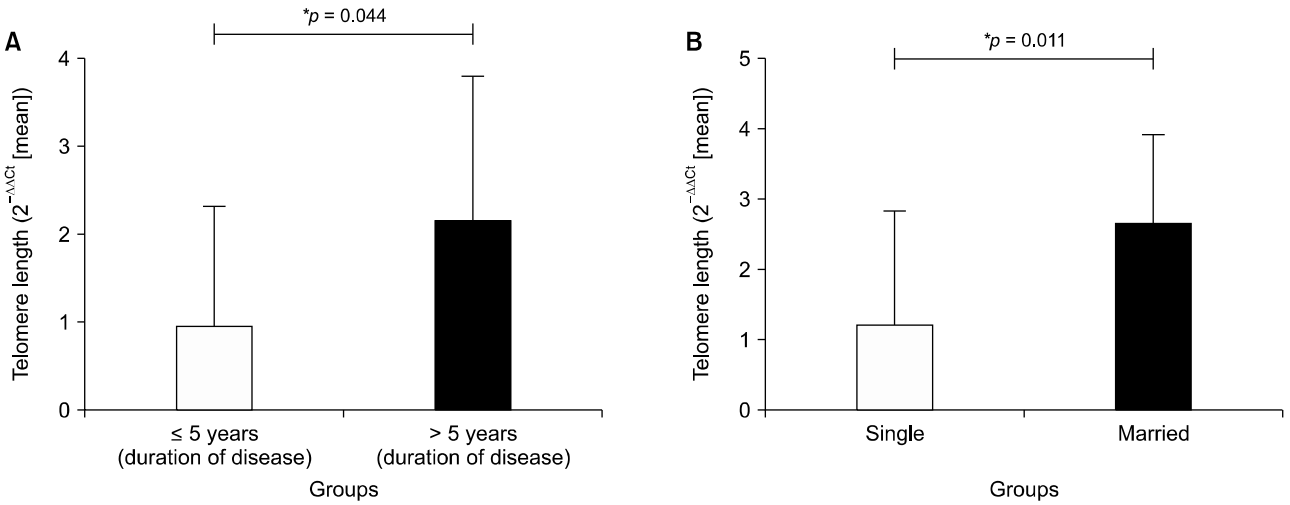

Fig. 3. (A) Relation of patients' telomere length and duration of disease. (B) Relation of patients' telomere length and marital status.
*Means statically significant.

longer than 5 years had longer telomere length than patients treated shorter than 5 years ($p > 0.05$). Type of antipsychotic medication had no significant effect on telomere length, too ($p > 0.05$). But patients using aripiprazole had longer telomere when compared with other antipsychotic users.

ATPase6 Mutations and Telomere Length in Schizophrenia Patients

There was an association between mutations and telomere length ($p = 0.001$) (Fig. 4). Telomere length of patients with G8697A mutation was longer compared with patients carrying other mutations. Patients carrying A8860G mutation had the shortest telomere in all patients.

DISCUSSION

Impairment of mitochondrial functions and cellular senescence has a link with telomere shortening [25]. Shortening telomere length detected in schizophrenia is consistent with abnormal aging related to the disease [17]. Investigating brain tissues of schizophrenia patients revealed different energy metabolism, oxidative stress, and mitochondrial gene expression [8,9] in schizophrenia than in control [7]. In the study, we evaluated the relation of telomere length and *ATPase6* mutations in 34 Turkish schizophrenia patients. To determine telomere length and *ATPase6* mutations, qRT-PCR and Sanger sequencing were used, respectively. Results of the mutation analysis showed that mutation rate of samples was 100%. There was a significant relation with mutation type and telomere length. We approved the studies [26-30] that demonstrated shorter telomere length in patients with schizophrenia than healthy controls. Telomere length of patients who diagnosed more than five years were longer than telomere length of patients diagnosed less than 5 years. Besides, married schizophrenia patients had longer telomere than single patients.

There were several studies investigating mitochondrial DNA variants in schizophrenia patients [31-35] (Table 4). Torrell *et al.* [36] investigated mitochondrial variants in schizophrenia patients and found no pathogenic mtDNA mutation. They determined two schizophrenia related variants. However the variants did not show any relation with neither phenotypic characteristic of schizophrenia nor mitochondrial function [36]. Bi *et al.* [32] analyzed schizophrenic families and suggested some mitochondrial mutations confer risk to schizophrenia pathogenesis and contribute to mitochondrial dysfunction. In this study sequencing the *ATPase6* gene of 34 schizophrenia patients showed that A8860G mutation was more common than other mutations in our patients. We did not find any relation between mutations type and patient characteristics. Some mutations may not lead to remarkable alterations in patients' characteristics. The discrepancy of mutations type and patients are other factors determining the difference among studies.

The link between schizophrenia and telomere length has been an investigation point for many studies. Some of them suggested a relation of shorter telomere length and schizophrenia [26-30] (Table 5) on the contrary other researchers demonstrated longer telomere length in schizophrenia patients [37-41]. There are conflicting results so it

Table 5. Published studies related with telomere length in schizophrenia

Literature	Patients' telomere length	Patients number
Zhang *et al.* [37], 2018	Longer	1,241
Kota *et al.* [26], 2015	Shorter	71
Rao *et al.* [27], 2016	Shorter	141
Nieratschker *et al.* [38], 2013	Longer	539
van Mierlo *et al.* [28], 2017	Shorter	2
Maurya *et al.* [39], 2018	Longer	154
Galletly *et al.* [29], 2017	Shorter	48
Malaspina *et al.* [40], 2014	Longer	53
Monroy-Jaramillo *et al.* [30], 2017	Shorter	170
Cui *et al.* [41], 2017	Longer	126

Table 4. Studies investigating mtDNA variants in patients with schizophrenia in the literature

Literature	Published mtDNA genes	Number of samples	Number of variants
Bertolin *et al.* [31], 2011	*ATPase6, COII*	89	215
Ueno *et al.* [35], 2009	*ATPase6*	93	220
Martorell *et al.* [34], 2006	*ATPase6, ND1-5, CO1-3, CYB*	6	50
Ivanova *et al.* [33], 2021	*ND1-5*	60	480
Bi *et al.* [32], 2016	Data not available	11	17

has been still needed to be clearer. Our investigation results showed meaningful differences in the telomere length between schizophrenia and healthy controls. The shorter telomere length of schizophrenic patients may be a result of stress or abnormal aging [17] distinct from the disease itself.

Mitochondrial changes contribute to telomere shortening since the effects of increasing ROS on telomere DNA [10-12]. Abnormal aging related to schizophrenia [17] may be a result of mitochondrial dysfunction and increasing senescence accompanying telomere shortening [25]. Zhou *et al.* [42] showed shorter telomere length in patients with mitochondrial mutation than healthy controls. In our study patients with different mitochondrial mutations represented different telomere lengths. Patients with A8860G mutation had shorter telomere than other patients who had other mutations. Telomere length of patients with G8697A mutation was longer than others. Differences between studies may cause from different patient populations or different mutations type that was determined. Relation of mitochondria and telomere has been shown directly or indirectly [10-12,42]. However, this is the first study underlined relation of *ATPase6* mutations and telomere length in Turkish schizophrenia patients.

Association of smoking and telomere length was investigated before and telomere shortening and smoking have not had any relation [43]. Balzan *et al.* [44] studied link of alcohol and cigarette consumption and telomere length among schizophrenia patients and did not find any relation. In line with the study we did not found any significant link between smoking and telomere length however smoking patients had shorter telomere length than others. Smoking was more often among patients than controls which may affect telomere length. Marital status of patients may affect their relation with social environment and may cause change of telomere length. Yen and Lung [45] revealed relation of longer telomere length and marriage. Balzan *et al.* [44] suggested schizophrenia patients who live alone had shorter telomere length than patients live with family. In harmony with the studies, we found that married patients had longer telomere than single patients. This can be a result of diminishing stress by marriage or increasing social interaction in the family.

In schizophrenia patients' telomere length is affected by many conditions. A study with chronic schizophrenia and early schizophrenia patients suggested a relation of shorter telomere length and longer disease duration [46]. In our study patients with disease duration more than five years had longer telomere length than patients with shorter disease durations. This discrepancy may cause by the variability of patient population or treatment efficiency that was not mentioned. Treatment of the disease by medication can also cause telomere length alteration. Some researchers pointed that psychotropic medications may have anti-oxidative effects and thus prevent telomere attrition [47,48]. A study including schizophrenia patients treated with different twelve antipsychotics including aripiprazole, olanzapine, clozapine revealed a relation between olanzapine and shorter telomere [30]. Yu *et al.* [48] suggested patients who had a good response to treatment showed longer telomere length. However, in our study, we did not find significant relation between medication and telomere length but patients using Paliperidone had shorter telomere than telomere of patients using other antipsychotics. To measure telomere length before and after treatment may give more information about effect of medication on telomere length. Besides that, increasing telomere length may have been linked with duration of treatment or response to treatment.

The strength of this study is that we evaluated the *ATPase6* mutations in patients and telomere length both in patients and controls. We also evaluated telomere length among the patient group by comparing married and unmarried participants, duration of treatment etc. There were several limitations in the present study. First is that the number of subjects was small. Second limitation is that we could not investigate other mitochondrial mutations including *ND1-5*, *CO1-3*, *CYB*. Furthermore, since there were reluctant patients, we could not reach the targeted number of patients and the characteristics of some patients.

Telomere length and mitochondrial mutations were studied separately earlier, however, their relation was not investigated. This is the first study to reveal the relation between *ATPase6* mutation and telomere length in schizophrenia patients. Our results suggested that telomere length and mitochondrial mutations had an association. Telomere length shortening may be a result of *ATPase6* gene mutations in schizophrenia or vice versa. Telomere length and/or *ATPase6* mutations have become a candidate for the molecular marker to discriminate the schizophrenia. Discrepancies between studies may be the result of varied subject demographics (e.g., age, gender, and socioeconomic

status) [49]. Despite all these alterations, attrition of telomere length and determining of gene mutations may contribute to understanding clinical practices of schizophrenia patients [49]. Using a larger patient population and investigation of other mitochondrial mutations may help to better understand molecular changes in schizophrenia.

Limitations

The low number of participants is the main limitation of our study.

■ Funding

None.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Sevgi Karabulut Uzunçakmak, Ebubekir Dirican. Data acquisition: Halil Ozcan, Ugur Takim. Formal analysis: Sevgi Karabulut Uzunçakmak. Writing original draft: Sevgi Karabulut Uzunçakmak. Writing review & editing: Sevgi Karabulut Uzunçakmak, Ebubekir Dirican.

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