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Investigation of Survivin Promoter -31 G/C Polymorphism and Survivin Levels in Acromegaly

Akromegalide Survivin Promoterinin -31 G/C Polimorfizmi ve Survivin Düzeylerinin Araştırılması

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Abstract

Objevtive: Acromegaly is a rare disease characterized by growth hormone hypersecretion generally arising from pituitary adenomas. Survivin, an apoptosis inhibitor protein, plays an important role in cell cycle regulation and possibly involves hypophysis gland proliferation mechanisms. However, the underlying causes of somatotroph adenomas with different behaviors and useful prognostic markers are still not fully understood. We investigated possible associations between survivin gene promoter -31 G\C genotypes and serum survivin level and clinical prognostic factors in acromegaly. **Material and Methods:** Sixty-eight acromegaly patients and 171 age-sex matched control subjects were enrolled in the study. Survivin -31 G\C polymorphism was performed by using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Blood GH and IGF1 levels were assayed using a chemiluminescence immunometric assay. Serum survivin levels were determined by ELISA. **Results:** Acromegaly patients had significantly higher serum survivin levels than controls (p=0.001). We found no significant association between acromegaly patients and controls in terms of survivin gene promoter -31 G\C genotype distribution and allele frequencies. No correlation was found between disease characteristics and survivin gene polymorphisms. **Conclusion:** Our study suggests that serum survivin levels might be associated with acromegaly, but survivin -31 G\C polymorphisms do not modify individual susceptibility to acromegaly in the Turkish population.

Keywords: Acromegaly; polymorphism; survivin

Özet

Amaç: Akromegali, genellikle hipofiz adenomlarından kaynaklanan büyüme hormonu hipersekresyonu ile karakterize nadir görülen bir hastalıktır. Apoptozun bir inhibitör proteini olan survivin, hücre döngüsü düzenlemesinde önemli bir rol oynar ve hipofiz bezi proliferasyon mekanizmalarında yer alabilir. Farklı davranışlara sahip somatotrof adenomlarının gelişme mekanizmaları tam olarak anlaşılamamış ve kullanışlı prognostik faktörler saptanamamıştır. Bu çalışmada amacımız, survivin gen promotörü -31 G\C genotipleri ve ayrıca serum survivin düzeyi ile akromegalide klinik prognostik faktörler arasındaki olası ilişkiyi araştırmaktı. **Gereç ve Yöntemler:** Çalışmaya 68 akromegali hastası ve 171 yaş-cinsiyet uyumlu kontrol hastası dâhil edildi. Survivin -31 G\C polimorfizmi, bir polimeraz zincir reaksiyonu sınırlama fragmanı uzunluk polimorfizmi [polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)] kullanılarak gerçekleştirildi. Kan GH ve IGF1 seviyeleri, bir kemiluminesans immünometrik test kullanılarak analiz edildi. Serum survivin düzeyleri ELISA ile belirlenmiştir. **Bulgular:** Akromegali hastalarında serum survivin düzeyleri kontrol grubuna göre anlamlı derecede yüksekti (p=0,001). Akromegali hastaları ile survivin gen promotörü -31 G\C genotipi ve allel frekanslarının dağılımı için kontroller arasında anlamlı bir ilişki bulunamadı. Hastalık özellikleri ile survivin gen polimorfizmleri arasında korelasyon bulunmadı. **Sonuç:** Çalışmamız, serum survivin düzeylerinin akromegali ile ilişkili olabileceğini, ancak survivin -31 G\C polimorfizmlerinin Türklerden oluşan bir popülasyonda akromegali açısından bireysel duyarlılığı değiştirmediğini göstermiştir.

Anahtar kelimeler: Akromegali; polimorfizm; survivin

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Introduction

Acromegaly is a rare disease with a prevalence of 40-70 cases per million population and an annual incidence of 3-4 new cases per million population (1). Hypersecretion of growth hormone (GH), which is usually caused by pituitary adenoma, leads to progressive disfigurement mainly involving the face and extremities, especially in the soft tissue. Except for familial pituitary syndromes, limited studies have observed the association between genetic structure and sporadic pituitary tumors secreting GH. Sporadic tumors secreting GH generally arise from a somatotrope cell allowing clonal expansion (2,3). About one-third of somatotroph tumors have somatic mutations in the guanine nucleotide-binding α-subunit 1 gene, leading to cellular proliferation and GH hyperfunction (4,5). Several studies have also determined single nucleotide polymorphisms such as exon-3 deleted GH receptor and aryl hydrocarbon receptor-interacting protein gene and attributed to long term complications of acromegaly (6-8). Although familial pituitary syndromes such as multiple endocrine neoplasia type 1 have been widely studied, the genetic basis of the sporadic somatotrophs (9).

Survivin is regarded as an apoptosis inhibitor protein, which plays an important role in cell cycle regulation (10,11). Survivin causes negative regulation of programmed cell death by acting as an inhibitor of caspase activation (12). The overexpression of survivin is associated with several malignancies and poor prognosis in colorectal cancer, lung cancer, pancreatic cancer, and hepatocellular carcinoma (13-15), and can play a crucial role in tumorigenesis. Although survivin was recently shown to be expressed in normal pituitary tissue and overexpressed in pituitary adenomas, its role in the development and course of acromegaly is yet unexplored (16,17).

This study investigated whether survivin polymorphism and serum survivin levels have a role in the development of acromegaly in the Turkish population. In addition, correlations between survivin gene polymorphisms, serum survivin levels, and tumor size and their influence on the remission of acromegaly were studied.

Material and Methods

Patients and Hormone Assays

Sixty-eight acromegaly patients and 171 control subjects were recruited for this study in the Endocrinology Clinic of Bezmiâlem University Hospital between 2012 and 2015. The mean age of the acromegaly group was 45±1.73 years, and that of control was 42.92±2.11 years. The mean age at diagnosis was 39.88±1.7 years.

Acromegaly was diagnosed using serum GH, which could not be suppressed to <1 ng/mL during oral glucose tolerance test and age- and gender-matched high serum IGF1 levels (18). Hypophysis magnetic resonance imaging was performed on all acromegalic patients, and the maximum diameter obtained from the data was determined as the tumor size. Nine patients were diagnosed in other centers, and tumor size before treatment of these patients was lacking. Patients with acromegaly, controlled under disease-specific treatment (lanreotide or octreotide), and those with post-operative cure were included in the controlled patient group. Serum IGF1 values were adjusted according to the percentage of the upper limit of normal (ULN) using the formula ($100*C_{IGF1}/ULN_{IGF1}$). Acromegaly patients are considered to be in biochemical remission when basal GH is under 1 ng/mL and IGF1 level 1.2 x ULN.

Healthy volunteers between 18-65 years of age and without a history of chronic disease or medication use were included in the age- and gender-matched control group.

Blood GH and GF1 levels were assayed using chemiluminescence immunometric assay (Siemens Advia-Centaur USA). Age-related reference ranges for IGF1 were: 18-20 y: 197-956; 20-23y: 215-628; 23-25y: 169-591; 25-30y: 119-476; 30-40y: 100-494; 40-50y: 101-303; >50y: 78-258 (ng/mL).

Bezmialem Vakıf University Clinical Research Ethics Committee approved this study with the number of 71306642/050-01-04/64 and dated 11.3.2013, and all procedures were conducted in accordance with the Helsinki Declaration.

DNA isolation

Blood samples were collected in tubes containing EDTA. A standard salting procedure was used to isolate genomic DNA (19).

Genotyping

Genotyping studies were performed by using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The -31G\C polymorphisms in the promoter region of the survivin gene were examined using 0.25 µM of each primer shown in Table 1 for the reaction in a volume of 25 µL containing, 1.5 mM MgCl2, 50 mM KCl, 10 mM Tris-HCl, pH 8.4, 0.16 mM of each deoxyribonucleotide triphosphate (MBI Fermentas), and 1 U Taq polymerase (MBI Fermentas). Amplification was carried out using the following protocol: initial denaturation at 94 °C for 5 min; followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 52 °C for 30 s, and extension at 72 °C for 30 s, and a cycle final extension at 72 °C for 10 min (19). The PCR product exhibited a 329-bp fragment indicating the -31G/C region polymorphism. PCR product (10 µL) was digested with *Bcn*I (MBI Fermentas). Samples were repeated if a conflict occurred. The expected results after the restriction digestion for each gene fragment are given in Table 1.

Survivin Assay

Fresh-blood samples were immediately centrifuged at 3000 rpm for 5 min to separate serum, and samples were kept frozen at -20 °C until the study. Serum survivin levels were determined with a commercially available sandwich ELISA kit (Platinum ELISA, Bender MedSystems GmbH, Vienna).

Statistical Analysis

Statistical analyses were performed using SPSS version 11.0 for Windows (SPSS Inc. Chicago, IL, USA). Differences in the frequency of the survivin -31 G/C polymorphism between acromegaly patients versus the control group and clinical data within the acromegaly subgroup were analyzed using the Chi-square test. The Hardy-Weinberg equilibrium was tested for all polymorphisms. Numeric values were evaluated by the Student's t-test and Mann-Whitney U test. The relative associations between acromegaly patients and controls were assessed by calculating odds ratios (ORs) and 95% confidence intervals (95% CIs). The threshold for significance was $p<0.05$.

Results

Table 2 shows the demographic characteristics of acromegaly patients and the control group. In the acromegaly group, mean GH, IGF1 levels, and IGF1 norm were 16.0±2.3 ng/mL, 842±48.9 ng/mL, and 321.1±17.3% before treatment, respectively. Forty-six (78%) patients had macroadenoma at the time of diagnosis. After treatment, mean GH, IGF1 levels, and IGF1 norm decreased to 1.3±0.2 ng/mL, 247±19.8 ng/mL, and 104.2±9.2%, respectively. Mean tumor size after treatment was <1 cm in 41 (80.4%) acromegaly patients, and 43 (78.2%) patients were in biochemical remission. The mean survivin level was slightly higher at 34.5±0.6 in acromegaly patients and 32.4±1.3 in control subjects ($p=0.001$).

Genotypes and allele frequencies for survivin -31G\C polymorphism in acromegaly patients and controls were listed in <Table 3. Genotype distributions for survivin -31 G/C polymorphism in control and patient

Table 1. PCR-RFLP Producers and Products of Survivin-31 G\C Polymorphism.

	Primers	PCR product	Restriction Enzyme	Restriction Product
-31 G\C (rs9904341)	F:5′ -CGTTCTTTGAAAGCAGTCGAG-3′ R:5′ -TGTAGAGATGCGGTGGTCCT-3′	329 bp	Bcnl	CC: 329 bp CG: 329/234/92 bp GG:234/92 bp

bp: Base pair; F: Forward; R: Reverse.

Table 2. Demographic characteristics of acromegaly patients and control group.

	Acromegaly	Control
Gender (n/%)		
Female	40 (%59)	110 (%64.3)
Male	28 (%41)	61 (%35.7)
Age (y)	45.0±1.7	42.9 ±2.1
Age Onset (y)	39.8±1.7	
Tumor Size Before Treatment	n=59	
Macroadenoma	46 (%78)	
Microadenoma	13 (%22)	
Number of Resection		
0	16 (%23.5)	
1	42 (%61.8)	
≥2	10 (%14.7)	
IGF1 (ng/mL)		
IGF1 Before Treatment	842.9±48.9	
IGF1 After Treatment	247.7±19.8	
IGF1 norm		
%ULN Before Treatment	321.1±17.3	
%ULN After Treatment	104.2±9.2	
GH		
GH Before Treatment	16.0±2.3	
GH After Treatment	1.3±0.2	
Remission Status	n=55	
Controlled	43 (%78.2)	
Uncontrolled	12 (%21.8)	
Tumor Size After Treatment	n=51	
≥1 cm (n/%)	10 (%19.6)	
<1 cm (n/%)	41 (%80.4)	
Survivin Level (pg/mL)*	34.5±0.6	32.4 ±1.3

Mean values±standard error; *p=0.001 (Mann-Whitney U test); IGF1: Insulin-like growth factor 1; GH: Growth hormone; ULN: Upper Limit of Normal Range.

groups were in agreement with the Hardy Weinberg equilibrium (p=0.197; p=0.335, respectively). Survivin -31 G\C genotypes and allele frequencies between acromegaly patients and controls were not statistically significant (p=0.73; p=0.46, respectively).

Table 4 shows the comparison of the characteristics of acromegaly patients according to survivin genotypes. No significant difference in genotype distribution was observed between patients with microadenomas (<1 cm) and macroadenomas (≥1 cm) (p=0.32). All 26 patients who had 3-fold higher IGF1 levels than ULN before treatment were carrying the G allele, but the difference was not statistically significant (p=0.068) (Data not shown). All ten patients operated at least two times, and 91.7% of the patients with uncontrolled disease activity were carrying the G allele (p>0.05). No association was found be-

Table 3. Genotypes and allele frequencies for survivin genotypes in acromegaly patients.

Genotype	Patients n (%)	Controls n (%)
GG	28 (41.2%)	63 (36.8%)
CG	34 (50%)	88 (51.5%)
CC	6 (8.8%)	20 (11.7%)
p value >0.05		
Alleles		
G	90 (66.2%)	214 (62.6%)
C	46 (33.8%)	128 (37.4%)
p value >0.05		

Table 4. Characteristics of acromegaly patients according to survivin genotype.

	GG	CG	CC
Gender (n)			
Female	15	19	6
Male	13	15	0
Age onset (y)	37.5±12.1	43±16.1	33.5±9.9
GH (ng/mL)			
Before Treatment	19.6±15.6	13.5±15.4	10.6
After Treatment	1.5±1.5	1.3±1.4	0.9±0.5
IGF1 (ng/mL)			
Before Treatment	831.3±295.5	858.7±373.4	780.9±229.9
After Treatment	225.3±107.9	279.0±183.2	207.0±105.1
IGF1 norm			
%ULN Before Treatment	305.3±119.4	340.9±119.5	257.5±23.7
%ULN After Treatment	95.0±40.2	116.2±87.8	89.1±54.3
Tumor Size Before Treatment (cm)			
<1	4	7	2
≥1	20	24	2
Number of Adenoma Resections (n)			
0	3	6	0
≤1	16	14	6
≥2	5	5	0
Tumor Size After Treatment (cm)			
≤1	18	18	5
≥1	5	5	0
Remission			
+	20	18	5
-	4	7	1
Survivin Level (pg/mL)	35.0±4.2	34.0±4.8	34.3±5.4

Mean values±standard error; *p=0.001 (Mann-Whitney U test); IGF1: Insulin-like growth factor 1; GH: Growth hormone; ULN: Upper Limit of Normal Range.

tween the distribution of survivin genotypes and pre-post treatment GH, IGF1 levels, and remission status. Additionally, there was no significant relationship between treatment options and survivin polymorphism and levels.

Discussion

Survivin has attracted much interest in cancer research studies due to its essential role in tumorigenesis initiation and progression. It is an apoptotic inhibitor protein, which regulates caspases and programmed cell death (20). The survivin gene is located on chromosome 17q25, and the most widely studied polymorphism of the survivin gene is the G to C substitution at position -31 (survivin -31G>C, rs9904341) (21). To our knowledge, this is the first study to investigate the distribution of survivin -31 G/C polymorphism and survivin levels in acromegaly.

In the present study, no difference was observed in the distribution of survivin -31G/C genotypes between acromegaly and control subjects. We found similar results for the distribution of -31G/C genotypes to those reported by Bayram et al. in the Turkish population (22). Our results were consistent with previous findings wherein there was no association between the -31G/C polymorphism and development risk for several cancer types such as renal cell and esophageal carcinoma (23,24). In patients with overexpressed survivin mRNA, no significant difference might be found in the distribution of -31G/C genotypes (25). On the other hand, survivin -31 G/C polymorphism was associ-

ated with an increased risk of developing many tumors (26-28). This situation may be explained in terms of differences in the study population, environmental, and ethnic factors (22).

To date, several chromosomal lesions have been reported in sporadic somatotroph adenomas. Loss of heterogeneity in chromosomes 11q13, 13, and 9 have been associated with 20% of sporadic acromegaly cases (29,30). Additionally, Gsp, Ras, and pituitary tumor transforming gene (PTTG) mutations were shown to be responsible for the development and possible behaviors of pituitary tumors in a subset of cases (31-33). However, genetic mechanisms involving disease development and course are still not known in most acromegaly cases. Besides, the survivin transcription level is possibly modified positively by the presence of survivin genotype C allele (26). Its prognostic value in human neoplasms has not been clarified yet. In a study from Turkey, Ademoglu et al. observed higher serum survivin levels in the acromegaly patients than in the control group, but the difference was not statistically significant (17). Likewise, we found that serum survivin levels were higher in acromegaly patients than in control subjects. Survivin expression could play an essential role in regulating hypophysis gland proliferation (34) and delay cell death (21). Jankowska et al. demonstrated that survivin expression was six-fold higher in tumor tissue than in normal pituitary (16). Overexpression of survivin has also been demonstrated in solid tumors and is related to higher proliferative markers and poor prognosis (35,36).

Our study showed that survivin -31 G/C polymorphism and survivin levels were not associated with clinical characteristics of acromegaly such as tumor size, hormone levels, and acromegaly disease phase.

The study's limitation was that it was a cross-sectional and hospital-based case-control study. Therefore, patients were included at a single center and may not represent acromegaly patients in the general population. However, it must be noted that acromegaly is a rare disease, and our center is a reference hospital that admits patients from all over the country.

In summary, it can be suggested that survivin -31G\C polymorphisms do not modify individual susceptibility to the acromegaly. In this study, no association was observed between disease characteristics (such as tumor size, hormone levels, and remission status) and survivin polymorphism in surviving gene, although increased survivin levels were observed in acromegaly patients compared to that in healthy subjects. However, the molecular effects of these different single nucleotide polymorphisms on the functional mechanism of surviving in tumorigenesis have not yet been clarified, and the involved mechanisms need further studies.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Muzaffer İlhan, İlhan Yaylım, Ertuğrul Taşan; Design: Seda Turgut, Muzaffer İlhan, Gurbet Korkmaz; Control/Supervision: Özcan Karaman, Ertuğrul Taşan, İlhan Yaylım; Data Collection and/or Processing: Seda Turgut, Gurbet Korkmaz, Nazlı Ezgi Özkan, Muzaffer İlhan, Saime Turan; Analysis and/or Interpretation: Nazlı Ezgi Özkan, İlhan Yaylım, Muzaffer İlhan; Literature Review: Seda Turgut, Saime Turan; Writing the Article: Muzaffer İlhan, Seda Turgut, İlhan Yaylım; Critical Review: Özcan Karaman, Muzaffer İlhan, Gurbet Korkmaz, Seda Turgut; References and Fundings: Ertuğrul Taşan; İlhan Yaylım; Materials: Muzaffer İlhan, İlhan Yaylım, Ertuğrul Taşan.

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