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Association between acromegaly and a single nucleotide polymorphism (rs543019827, rs547640100, rs545558970, rs2453837, and rs6953668 A/G) in the IGFBP3 gene in Iraqi Acromegaly Diabetic Patients

Hend Majed Muhsen[1]*, Rana S. Jawad[1], Noor Thair Tahir[2]
[1]Mustansiriyah University, College of Science / Iraq.
[2]National Diabetes Center, Mustansiriyah University, Baghdad, Iraq.
***Corresponding author:** Hend Majed Muhsen, Mustansiriyah University, College of Science / Iraq, Email: hend.mjd.2018@gmail.com

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ABSTRACT

Objective: This study aimed Study the genetic polymorphism of the IGFBP-3 gene that is responsible for the synthesis of IGFBP3 protein and its association with acromegaly patients.

Methods: This study was done at the National Diabetes center/Mustansiriyah University between October 2021 and the end of April 2022. Nighty participate in this study (50) acromegaly diabetic patients and (40) healthy control compared patients. In this study, Genomic DNA was extracted then genotyping was performed to detect the single nucleotide polymorphisms (SNPs) in the IGFBP-3 gene using a specific primer.

Results: This is the first study to give frequency distribution genotypes of the IGFBP-3 gene in patients with active acromegaly in Iraq, The IGFBP-3 gene promoter selected region consists of 440 bp, which is highly suspected as a transcription factor binding site (TFBS), and was subjected to DNA sequencing to detect SNPs (point mutations) that might affect to cause disease. These sequences were scanned in 20 individuals, 15 of whom were acromegaly patients and 5 of whom were controls, only five SNPs in the IGFBP-3 gene were selected (rs543019827C/T, rs547640100C/T, rs545558970A/G, rs2453837 C/T, and rs6953668 A/G). The sequence data of 20 samples demonstrated that (rs543019827 C/T, rs545558970 A/G, and rs6953668 A/G) SNPs in the IGFBP-3 gene showed significantly different frequencies of heterozygous genotype (P-value <0.05).

Conclusion: In (rs543019827 C/T) SNP the odds ratio for the CT genotype was 16, in (rs545558970 A/G) SNP the odds ratio for the AG genotype was 4.13, and in (rs6953668 A/G) SNP the odds ratio for the AG genotype was 1.83, this means that person who caring these genotypes have a higher risk for disease than other genotypes.

Keywords: *Acromegaly, IGFBP-3 gene, rs543019827C/T, rs547640100C/T, rs545558970A/G, rs2453837 C/T, and rs6953668 A/G*

INTRODUCTION

Acromegaly is an uncommon condition caused by high levels of growth hormone (GH) and insulin-like growth factor type I (IGF-I), and it is linked to several long-term comorbidities (Kasuki et al., 2020). Acromegaly is a chronic debilitating illness in adults that is under-recognized and underdiagnosed and is linked to increased morbidity and death. A growth hormone (GH)-secreting pituitary tumor is virtually always the cause. Life expectancy is lowered by several years in untreated persons with or without co-morbidities. Successful treatment leads to restoration to normal life duration. Acromegaly usually appears between the ages of 25 and 40, however, diagnosis is sometimes delayed for several years. The median age upon diagnosis is between 40 and 50 years old (Stiles et al., 2021). When mortality reasons are examined, it is shown that 15% of neoplasias, 25% of respiratory diseases, and 60% of cardiovascular diseases account for the deaths of acromegalic individuals (Bembi, 2020). GH and IGF-I both have significant effects on metabolism and growth. GH is necessary for postnatal development in all species, but it also has significant side effects on immunological function, muscle function, energy metabolism, body composition, bone metabolism, immune system, and the central nervous system (CNS), which can impact things like hunger, cognition, and sleep. IGF-I plays a crucial role in tissue regeneration and repair processes as a mitogen and activator of cell proliferation. Additionally, it mediates a few of GH's anabolic and growth-promoting functions. IGF1 is produced in the liver and various peripheral organs as a result of GH secretion. IGF-specific binding proteins (IGFBPs) bind to about 99% of the circulating IGF1, altering its bioavailability by lengthening its half-life and modifying its pharmacological effects on target tissues. More than 75% of serum IGFs are transported by IGFBP3, the most prevalent circulating subtype (Caputo et al., 2021). Polymorphisms in the promoter regions of the IGFBP3 genes recently described genes that are encoded on chromosome 7p. In theory, these polymorphisms might affect the clinical manifestation and treatment approaches in acromegaly (Ramos-Leví et al., 2015). Early research showed that at least pituitary-dependent GH excess could be a hereditary disease because acromegalies were usually known to have an inherited disorder that ran in their families (Daly et al., 2019).

Insulin-like growth factor binding protein -3 gene, this gene is a member of the insulin-like growth factor binding protein (IGFBP), additionally known as (IBP3, BP-53) which encodes a protein that has the IGFBP and thyroglobulin type I domains. The protein forms a ternary complex with either insulin-like growth factor (IGF) I or II and the insulin-like growth factor acid-labile subunit (IGFALS). It circulates through the plasma, extending IGFs' half-lives and changing how they interact with cell surface receptors. Different isoforms are encoded by alternative transcriptional splice variants, which have been described (Zhu et al., 2019). The single-copy human IGFBP-3 gene was located on chromosome 7. Making use of hybrid DNAs from somatic cells from hamsters and humans in a polymerase chain reaction. The human IGFBP-3 gene is 8.9 kb long and has 4 introns, as opposed to the three introns present in the IGFBP-1 and -2 genes (Garcia de la Serrana & Macqueen, 2018). The positions of the four introns in the human IGFBP-3 gene match those predicted by certain porcine cDNA clones with intron-like sequences (Cai et al., 2020).

Studies have discovered a connection between IGFBP3 single nucleotide polymorphisms and the risk of several types of cancer (Qin et al., 2016). Additionally, differences in the body's levels of IGFBP3 and IGF-1 have been connected to the polymorphisms of this gene (Bonilla et al., 2016). Another study discovered a connection between the risk of colorectal cancer and circulating IGFBP3 levels (Murphy et al., 2020).

MATERIAL AND METHODS

Nighty subjects in this study. ((50) acromegaly diabetic Patients (25 male and 25 female)) and ((40) healthy control (20) males and (20) females)) aged between (30-65years), who were attending the National Diabetes Center (NDC) / Mustansiriyah University and, during the period from November 2021 until the end of May 2022.

All data were collected about sex, age, weight, high, BMI, SBP, and DPB.

Blood samples from each participant were collected in tubes containing ethylene diamine tetraacetic acid (EDTA) and stored at −80◦C until use. Genomic DNA was extracted from peripheral white blood cells using EasyPure® Genomic DNA Kit (Trans Gen biotech, China). The DNA quantity was determined using a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA). Polymerase chain reaction (PCR) primer pairs were used to amplify IGFBP3: ACCAGCTTCTGTGCCTTACT (forward primer) and CTCCCTGACGCAGCATTAAC (reverse primer).

Statistical analysis of the results as shown by Rotor-Gene Q Series Software: For Independent samples, a t-test was used to compare the means of the studied groups. Hardy-Weinberg equilibrium (HWE) was used to investigate allele and genotype frequencies. The results were computed using a web-based tool (Rodriguez et al., 2009). The Chi-square test was used to compare the frequency of genotypes and alleles in the patient and control groups (c2test). Odds ratios (ORs) with a 95 percent confidence interval (CI) were constructed to determine the strength of the link between the investigated gene (IGFBP3) SNPs and control to analyze the possible relationships between genetic variations of (IGFBP3).

RESULTS

This is the first study in an Iraqi community to look at the relationship between acromegaly susceptibility and IGFBP-3 gene polymorphisms. To ensure genetic homogeneity among the respondents and to prevent the confounding effects of demographic differences in genetic origins and environmental variables, such as lifestyle choices, the study's population was restricted to the middle of Iraq. The current study investigates the polymorphism of IGFBP-3 genes among 40 apparently healthy and 50 patients from different areas of the middle of Iraq, the correlation between the polymorphism of the IGFBP-3 gene and various factors were studied. Then, in available databases, the IGFBP-3 polymorphisms were chosen (http://www.ncbi.nlm.nih.gov/snp/), including five SNPs (rs543019827C/T, rs547640100 C/T, rs545558970 A/G, rs2453837 C/T, rs6953668 A/G).

IGFBP3 gene polymorphism rs543019827 C/T

The SNP of IGFBP3 gene (rs543019827 C/T; situated on the chromosome 7:45916268 bp) had three genotypes shown to them (CC, CT, TT) that were corresponding to two alleles (C and T). Analysis of Hardy-Weinberg equilibrium (HWE) in the healthy group and acromegaly group revealed that the genotypes were consistent with the equilibrium, although the difference was not significant ($P > 0.05$) in the control group; there were significant variations ($p\ 0.04 < 0.05$) between the observed and expected genotype frequencies in the patient group. Table (1).

TABLE 1: Number and percentage frequencies of IGFBP3 gene SNP rs543019827 genotypes and their Hardy-Weinberg equilibrium (HWE) in the Control group and acromegaly group.

Groups rs543019827		Wild CC	Hetero CT	Mutant TT	X^2	p-value
Patients Genotype	Observed no. (%)	3	12	0	6.67	0.04 *
	Expected no. (%)	5.4	7.2	2.4		
ontrol GenotypeC	Observed no. (%)	4	1	0	0.06	0.97 N.S
	Expected no. (%)	4.05	0.9	0.05		
Total Observed		7	13	0		

χ 2, Chi-square.

IGFBP3 gene (rs543019827 C/T) SNP and Acromegaly Risk

Inspecting IGFBP3 gene (rs543019827 C/T) genotypes and allele frequencies in the acromegaly group and control group revealed that the homozygous and heterozygous genotypes frequency of C alleles showed significant variation in patients compared to control, there was a positive correlation (etiological factor) between CT genotype with acromegaly, the odds ratio for the CT genotype was 16 (95% CI, 1.22– 42.37), indicating that heterozygous genotype CT tended to be associated with an increased acromegaly risk in this group as indicated by odds ratios >1.

Additionally, a tendency for a significantly extremely high risk linked to the T-allele, as indicated by odds ratios > 1 was observed at 2.67 (95% CI, 0.50–20.67) Conversely, a trend for decreased acromegaly risk associated with the C allele, as indicated by odds ratios < 1, Table (2).

TABLE 2: Genotype and allele frequencies of IGFBP3 gene SNP rs543019827 of Control group and acromegaly group.

Genotypes Group rs543019827	Study Group		Odds Ratio (OR)	CI 95%	P value
	Patients	Control			
Wild CC	3(20.00%)	4(80.00%)	0.06	0.00 to 0.82	0.016*
Hetero CT	12(80.00%)	1(20.00%)	16	1.22 to 42.37	0.016*
Mutant TT	0	0	---	---	----
Total	15	5			
Alleles frequency					
C	18(60.00%)	9(90.00%)	0.38	0.05 to 2.01	0.362
T	12(40.00%)	1(10.00%)	2.67	0.50 to 20.67	0.362

CI, confidence interval.

IGFBP3 gene polymorphism rs547640100 C/T

The SNP of IGFBP3 gene (rs547640100 C/T; situated on the chromosome 7:45916275 bp) had three genotypes shown to them (CC, CT, TT) that were corresponding to two alleles (C and T). The genotypes were consistent with the Hardy-Weinberg equilibrium (HWE) in the healthy group and the acromegaly group, and no significant (P>0.05) discrepancies were found between the observed and expected genotypes in the patient and control groups, Table (3).

TABLE 3: Number and percentage frequencies of IGFBP3 gene genotype SNP rs547640100 and their Hardy-Weinberg equilibrium (HWE) in the control group and acromegaly group.

Group rs54640100		Wild CC	Hetero CT	Mutant TT	X^2	P-value
Patients Genotype	Observed no. (%)	8	7	0	1.39	0.49 N.S
	Expected no. (%)	8.82	5.37	0.82		
Control Genotype	Observed no. (%)	2	3	0	0.92	0.63 NS
	Expected no. (%)	2.45	2.1	0.45		
Total Observed		10	10	10	0	

χ 2 , Chi-square.

IGFBP3 gene (rs547640100 C/T) SNP and Acromegaly Risk

Inspecting IGFBP3 gene (rs547640100 C/T) genotypes and allele frequencies in acromegaly group and control group revealed that the homozygous and heterozygous genotype frequency of the C allele showed no significant variation in patients compared to the control, there was a negative correlation between CC and CT genotype with acromegaly odds ratios 0.58 (95% CI 0.06 – 5.17), the TC genotype tended to be associated with a decreased acromegaly risk in this group as indicated by odds ratios < 1.

In addition, there is a tendency for a markedly elevated risk linked to the C allele. As indicated by odds ratios > 1 was observed at 1.41 (95% CI 0.24–7.03), Although decreased frequencies of the C allele (76 vs. 70%) and increased frequencies of the T allele (23.33 vs. 30%) were observed in patients compared to controls and the difference was not significant, Table (4).

TABLE 4: Genotypes Group and allele frequencies of IGFBP3 gene SNP rs547640100 of Control group and acromegaly group.

Genotypes Group rs547640100	Study Group		Odds Ratio (OR)	CI 95%	P-value
	Patients	Control			
Wild CC	8(53.33%)	2(40.00%)	1.71	0.19 to 17.58	0.652
Hetero CT	7(46.67%)	3(60.00%)	0.58	0.06 to 5.17	0.652
Mutant TT	0	0	---	---	---
Total	15	5			
Alleles frequency					
C	23(76.67%)	7(70.00%)	1.41	0.24 to 7.03	0.545
T	7(23.33%)	3(30.00%)	0.71	0.14 to 4.21	0.545

CI, confidence interval.

IGFBP3 gene polymorphism rs545558970 A/G

The SNP of the IGFBP3 gene (rs545558970 A/G; situated on chromosome 7:45916343 bp) had three genotypes shown to them (AA, AG, and GG) that were corresponding to two alleles (A and G). No significant (P > 0.05) differences were found between the observed and expected genotypes in the patient and control groups, according to the evaluation of Hardy-Weinberg equilibrium (HWE) in the healthy group and the acromegaly group, Table (5).

TABLE 5: Number and percentage frequencies of IGFBP3 gene genotypes SNP rs545558970 and their Hardy-Weinberg equilibrium (HWE) in the control group and acromegaly group.

Groups rs545558970		Wild AA	Hetero AG	Mutant GG	X^2	P-value
Patients Genotype	Observed no. (%)	2	11	2	3.75	0.15 NS
	Expected no. (%)	3.75	7.5	3.75		
Control Genotype	Observed no. (%)	3	2	0	0.31	0.93 NS
	Expected no. (%)	3.2	1.6	0.2		
Total Observed		2	5	13	2	

χ 2, Chi-square.

IGFBP3 gene (rs545558970 A/G) SNP and Acromegaly Risk

Inspecting IGFBP3 gene (rs545558970 A/G) genotypes and allele frequencies in the acromegaly group and control group revealed that the homozygous AA genotype frequency of the A allele showed significant variation in patients compared to control (13 vs. 60 %; P = 0.039; OR= 0.10 ; 95%C.I. = 0.01 - 1.25), AG Polymorphism, the odds ratio for the AG genotype was 4.13 (CI 0.42-42.59) with p=0.202 indicating that heterozygous genotype AG was a higher risk of acromegaly condition than the wild type AA and mutant type GG.

Additionally, there is a tendency for the G-allele to significantly increase risk, as indicated by odds ratios >1 was observed at 4.00 (95% CI 0.75 – 30.53), Although the decreased frequency of A allele (50 vs. 80%) and increased frequency of the G allele (50 vs. 20%) was observed in patients compared to controls and the difference was no significant Table (6).

TABLE 6: Genotypes Group and allele frequencies of IGFBP3 gene SNP rs545558970 of the control group and acromegaly group.

Genotypes Group rs545558970	Study Group		Odds Ratio (OR)	CI 95%	P value
	Patients	Control			
Wild AA	2(13.33%)	3(60.00%)	0.10	0.01 to 1.25	0.039
Hetero AG	11(73.33%)	2(40.00%)	8.25	0.42 to 42.59	0.05*
Mutant GG	2(13.33%)	0(0.00%)	12	0.09 to30.45	0.724
Total	15	5			
Alleles frequency					
A	15(50.00%)	8(80.00%)	0.25	0.03 to 1.34	0.106
G	15(50.00%)	2(20.00%)	4.00	0.75 to 30.53	0.106

CI, confidence interval.

IGFBP3 gene polymorphism rs2453837 C/T

The SNP of IGFBP3 gene (rs2453837 C/T; situated on the chromosome 7:45916451 bp) had three genotypes shown to them (CC, CT, and TT) that were corresponding to two alleles (C and T). No significant (P > 0.05) differences were found between the observed and expected genotypes in the patient and control groups, according to the analysis of Hardy-Weinberg equilibrium (HWE) in the healthy group and the acromegaly group, Table (7).

TABLE 7: Number and percentage frequencies of IGFBP3 gene genotype SNP rs2453837 and their Hardy-Weinberg equilibrium (HWE) in the control group and acromegaly group.

Groups rs2453837		Wild CC	Hetero CT	Mutant TT	X^2	P-value
Patients Genotype	Observed no. (%)	3	11	1	3.65	0.16 NS
	Expected no. (%)	4.82	7.37	2.82		
Control Genotype	Observed no. (%)	2	2	1	0.14	0.93 NS
	Expected no. (%)	1.8	2.4	0.8		
Total Observed		5	5	13	2	

χ 2, Chi-square.

IGFBP3 gene (rs2453837 C/T) SNP and Acromegaly Risk

Inspecting IGFBP3 gene (rs2453837 C/T) genotypes and allele frequencies in the acromegaly group and control group revealed that the homozygous and heterozygous genotype frequency of the C allele showed no significant variation in patients compared to control, the odds ratio for the CT genotype was 4.13 (CI 0.42 – 42.59) with p=0.202 indicating that heterozygous genotype CT was a higher risk of acromegaly condition than the wild type CC and mutant type TT.

Additionally, a tendency for a significantly heightened risk linked to the T-allele, as indicated by odds ratios > 1 was observed at 1.15 (95% CI 0.26– 5.47). Although a decreased frequency of the C allele (56.6vs. 60%) and an increased frequency of the T allele (43.33 vs. 40%) were observed in patients compared to controls the difference was not significant , Table (8).

TABLE 8: Genotypes Group and allele frequencies of IGFBP3 gene SNP rs2453837of the control group and acromegaly group.

Genotypes Group rs2453837	Study Group		Odds Ratio (OR)	CI 95%	P value
	Patients	Control			
Wild CC	3 (20.00%)	2 (40.00%)	0.38	0.04 to 4.62	0.413
Hetero CT	11 (73.33%)	2 (40.00%)	4.13	0.42 to 42.59	0.202
Mutant TT	1 (6.67%)	1 (20.00%)	0.29	0.01 to 13.84	0.250
Total	15	5			
Alleles frequency					
C	17 (56.67%)	6 (60.00%)	0.87	0.18 to 3.88	0.858
T	13 (43.33%)	4 (40.00%)	1.15	0.26 to 5.47	0.858

CI, confidence interval.

IGFBP3 gene polymorphism rs6953668 A/G

The SNP of IGFBP3 gene (rs6953668 A/G; situated on the chromosome 7:45916276 bp) had three genotypes shown to them (AA, AG, and GG) that were corresponding to two alleles (A and G). No significant (P > 0.05) differences were found between the observed and expected genotypes in the patient and control groups, according to the assessment of Hardy-Weinberg equilibrium (HWE) in the healthy group and the acromegaly group, Table (9).

TABLE 9: Number and percentage frequencies of IGFBP3 gene genotypes SNP rs6953668 and their Hardy-Weinberg equilibrium (HWE) in the control group and acromegaly group.

Groups rs6953668		Wild AA	Hetero AG	Mutant GG	X^2	P-value
Patients Genotype	Observed no. (%)	4	11	0	5.03	0.08 NS
	Expected no. (%)	6.017	6.967	2.017		
Control Genotype	Observed no. (%)	2	3	0	0.92	0.63 NS
	Expected no. (%)	2.45	2.1	0.45		
Total Observed		6	14	0		

χ 2, Chi-square.

IGFBP3 gene (rs6953668 A/G) SNP and Acromegaly Risk

Inspecting IGFBP3 gene (rs6953668 A/G) genotypes and allele frequencies in the acromegaly group and control group revealed that the homozygous and heterozygous genotypes frequency of A alleles showed significant variation in patients compared to control, there was a positive correlation (etiological factor) between AG genotype with acromegaly (OR=1.83, CI= (0.16 – 16.78) with p=0.0437), this means that person who caring these genotypes have a higher risk for disease than GG genotypes.

In addition, the G-allele tends to be associated with a significantly heightened risk, as indicated by odds ratios > 1 was observed at 1.35 (95% CI 0.29 – 7.54). Although increased frequencies of the A allele (63.33 vs. 70%) and decreased frequencies of the G allele (36.67 vs. 30%) were observed in patients compared to controls and the difference was not significant, Table (10).

TABLE 10: Genotypes Group and allele frequencies of IGFBP3 gene SNP rs6953668 of Control group and acromegaly group.

Genotypes Group rs6953668	Study Group		Odds Ratio (OR)	CI 95%	P value
	Patients	Control			
Wild AA	4(26.67%)	2(40.00%)	0.55	0.06 to 6.24	0.0437*
Hetero AG	11(73.33%)	3(60.00%)	1.83	0.16 to 16.78	0.0437*
Mutant GG	0	0	----	-------	------
Total	15	5			
Alleles frequency					
A	19(63.33%)	7(70.00%)	0.74	0.13 to 3.50	0.859
G	11(36.67%)	3(30.00%)	1.35	0.29 to 7.54	0.859

CI, confidence interval.

DISCUSSION

In this study, These sequences were scanned in 20 individuals, 15 of whom were acromegaly patients and 5 of whom were controls, five SNPs in the IGFBP-3 gene were selected (rs543019827C/T, rs547640100 C/T, rs545558970 A/G, rs2453837 C/T, rs6953668 A/G) These SNPs were randomly selected from the gene.

The sequence data of 20 samples demonstrated that (rs543019827 C/T, rs545558970 A/G, and rs6953668 A/G) SNPs in the IGFBP-3 gene showed significantly different frequencies of heterozygous genotype (P-value <0.05). In (rs543019827 C/T) SNP the odds ratio for the CT genotype was 16, in (rs545558970 A/G) SNP the odds ratio for the AG genotype was 4.13, and in (rs6953668 A/G) SNP the odds ratio for the AG genotype was 1.83, this means that person who caring these genotypes have a higher risk for disease than mutant genotypes.

To our knowledge, the present study was the first investigation to identify the correlation between IGFBP-3 (rs543019827C/T, rs547640100 C/T, rs545558970 A/G, rs2453837 C/T, and rs6953668 A/G) polymorphisms, evaluating the higher risk of people with acromegaly.

The analysis in this study investigated whether IGFBP-3 inter-individual variation in Iraqi patients' susceptibility to acromegaly situations based on the earlier evaluation. Given that the risk of acromegaly linked with different gene variations varied depending on the proliferative state, the total risk of either disease outcome was connected to the individual genotypes.

According to several research, the IGFBP3 gene's further SNPs may decrease the risk of acromegaly. A recent article from (Gao et al.,

2018) . determines the effect of the rs2854744 A > C SNP at the −202 locus of IGFBP3 and whether it poses a risk for developing acromegaly. Reduced risk of acromegaly is linked to the C allele of rs2854744 (odds ratio 0.594, 95% confidence interval 0.388–0.909). In the Chinese population, women were more likely to exhibit this association. These findings revealed that IGFBP3 might contribute to the development of acromegaly. In a subsequent article, Gao and colleagues studied how the IGFBP3-202 A > C gene polymorphism affected patients with acromegaly's clinical characteristics and surgical outcomes. They found that whereas IGFBP3 polymorphisms may not have an impact on the metabolic or clinical aspects of growth hormone-secreting pituitary adenomas (GHPA) in acromegaly, they might affect hormone levels.

Akin et al, compared -202 A/C IGFBP3 genotypes with serum levels of glucose, insulin, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, GH, IGF-I, and IGFBP-3. They noticed that although there was no difference in the clinical presentation of patients with acromegaly, the frequency of -202 A/C IGFBP3 genotypes was substantially different between controls and patients. In a study from Jallad et al. (2015), except for GH levels following medication, which were noticeably lower in acromegaly patients bearing the A allele, they observed no correlation between -202 A/C IGFBP3 and clinical/hormonal characteristics and response to therapy (Akin et al., 2010).

In other research on genetic polymorphisms in the IGFBP3 gene, Liu et al, researchers looked at the relationship between the IGFBP3 variants rs2270628 C>T, rs10282088 C>A, rs3110697 G>A, and rs6953668 G>A. Hospital-based case-control research examined the relationship between SNPs and the risk of esophageal squamous cell carcinoma (ESCC) in the Chinese population. IGFBP3 rs2270628 C>T, rs10282088 C>A, and rs3110697 G>A were related to such a lower incidence of ESCC, according to multivariable logistic analysis. But there was no connection between the IGFBP3 rs6953668 G> A polymorphism and the risk of (ESCC) (Liu et al., 2015).

Liu and Chao, discovered that IGFBP3 rs2270628 C>T, rs3110697 G>A, and rs6953668 G>A and IGF2BP2 rs1470579 A>C, rs4402960 G>T A polymorphism may not increase the risk of non-small-cell lung cancer(NSCLC) in general. However, in stratified analyses, we discovered significant correlations between IGF2BP2 rs1470579 A>C, rs4402960 G>T polymorphisms and lowered risk of NSCLC in female, C, rs4402960 G>T polymorphisms and decreased risk of NSCLC in Asians (Gao et al., 2018).

The connection between the development of Esophagogastric junction adenocarcinoma (EGJA) and the SNPs for IGF2BP2 rs4402960 G > T, rs1470579 A > C, IGF1 rs5742612 A > G, and IGFBP3 rs3110697 G > A, rs2270628 C > T, and rs6953668 G > A was studied. discovered that the polymorphisms of IGF2BP2 rs1470579 A > C and IGFBP3 rs6953668 G > A may operate as protective factors for EGJA. They found that the polymorphism of IGFBP3 rs6953668 G > A may reduce the incidence of EGJA. In a different research, the impact of this SNP on controlling the expression of the IGFBP3 protein in EGJA patients' tissue was not explored (Tang et al., 2019).

Ren et al (2004), significant genetic variants in the IGFBP3 gene were linked to breast cancer risk in the Shanghai Breast Cancer study, and there was a relationship between IGFBP3 genotype and phenotype. According to these results, IGFBP3 polymorphisms may be a substantial genetic risk factor for breast cancer, with a connection between the chance of getting the disease and genotypes that had lower blood levels of IGFBP-3. Inferring the level of IGFBP-3 protein in the target tissues from genetic polymorphisms in the IGFBP3 gene may thus be more accurate than determining the level of IGFBP-3 protein in the blood (Ren et al., 2004).

CONCLUSION

According to the results of this study, genetic polymorphisms in the IGFBP3 genes are linked to an increased risk of developing acromegaly.

In this study, the IGFBP3 gene's polymorphism (rs543019827C/T, rs547640100C/T,

rs545558970A/G, rs2453837 C/T, and rs6953668 A/G) was analyzed, the sequence data of samples demonstrated that (rs543019827 C/T, rs545558970 A/G, and rs6953668 A/G) SNPs in the IGFBP-3 gene showed significantly different frequencies of heterozygous genotype (P-value <0.05). In (rs543019827 C/T) SNP the OR for the genotype CT was 16, in (rs545558970 A/G) SNP the OR for the genotype AG was 4.13, and in (rs6953668 A/G) SNP the OR for the genotype AG was 1.83, this means that person who caring these genotypes have a higher risk for disease than other genotypes.

REFERENCES

1. Akin, F., Turgut, S., Cirak, B., & Kursunluoglu, R. (2010). IGF (CA) 19 and IGFBP-3-202A/C gene polymorphism in patients with acromegaly. Growth Hormone & IGF Research, 20(6), 399–403.
2. Bembi, R. (2020). Oro-Dental Manifestations in Patients with Acromegaly: A Case Report. EC Dental Science, 19, 99–106.
3. Bonilla, C., Lewis, S. J., Rowlands, M., Gaunt, T. R., Davey Smith, G., Gunnell, D., Palmer, T., Donovan, J. L., Hamdy, F. C., & Neal, D. E. (2016). Assessing the role of insulin-like growth factors and binding proteins in prostate cancer using Mendelian randomization: Genetic variants as instruments for circulating levels. International Journal of Cancer, 139(7), 1520–1533.
4. Cai, Q., Dozmorov, M., & Oh, Y. (2020). IGFBP-3/IGFBP-3 Receptor System as an Anti-Tumor and Anti-Metastatic Signaling in Cancer. Cells, 9(5). https://doi.org/10.3390/cells9051261
5. Caputo, M., Pigni, S., Agosti, E., Daffara, T., Ferrero, A., Filigheddu, N., & Prodam, F. (2021). Regulation of GH and GH Signaling by Nutrients. Cells, 10(6), 1376.
6. Daly, A. F., Rostomyan, L., Betea, D., Bonneville, J.-F., Villa, C., Pellegata, N. S., Waser, B., Reubi, J.-C., Stephan, C. W., & Christ, E. (2019). AIP-mutated acromegaly resistant to first-generation somatostatin analogs: long-term control with pasireotide LAR in two patients. Endocrine Connections, 8(4), 367–377.
7. Gao, M., Zhu, B., Xu, Z., Liu, S., Liu, J., Zhang, G., Gao, Y., Fan, Y., & Kang, X. (2018). Association between acromegaly and a single nucleotide polymorphism (rs2854744) in the IGFBP3 gene. BMC Medical Genetics, 19(1), 1–7.
8. Garcia de la Serrana, D., & Macqueen, D. J. (2018). Insulin-like growth factor-binding proteins of teleost fishes. Frontiers in Endocrinology, 9, 80.
9. Kasuki, L., Antunes, X., Lamback, E. B., & Gadelha, M. R. (2020). Acromegaly: update on management and long-term morbidities. Endocrinology and Metabolism Clinics, 49(3), 475–486.
10. Liu, C., Tang, W., Chen, S., Wang, Y., Qiu, H., Yin, J., & Gu, H. (2015). IGFBP3 polymorphisms and risk of esophageal cancer in a Chinese population. International Journal of Clinical and Experimental Medicine, 8(9), 17006–17014.
11. Murphy, N., Carreras-Torres, R., Song, M., Chan, A. T., Martin, R. M., Papadimitriou, N., Dimou, N., Tsilidis, K. K., Banbury, B., & Bradbury, K. E. (2020). Circulating levels of insulin-like growth factor 1 and insulin-like growth factor binding protein 3 associate with risk of colorectal cancer based on serologic and Mendelian randomization analyses. Gastroenterology, 158(5), 1300–1312.
12. Qin, Z., Li, X., Tang, J., Jiang, X., Yu, Y., Wang, C., Xu, W., Hua, Y., Yu, B., & Zhang, W. (2016). Association between insulin-like growth factor-binding protein-3 polymorphism-202 A/C and the risk of prostate cancer: a meta-analysis. OncoTargets and Therapy, 9, 5451.
13. Ramos-Leví, A. M., Marazuela, M., Paniagua, A., Quinteiro, C., Riveiro, J., Álvarez-Escolá, C., Lucas, T., Blanco, C., De Miguel, P., De Icaya, P. M., Pavón, I., & Bernabeu, I. (2015). Analysis of IGF(CA)19 and IGFBP3-202A/C gene polymorphisms in patients with acromegaly: Association with clinical presentation and response to treatments. European Journal of Endocrinology, 172(2), 115–122. https://doi.org/10.1530/EJE-14-0613
14. Ren, Z., Cai, Q., Shu, X. O., Cai, H., Li, C., Yu, H., Gao, Y. T., & Zheng, W. (2004). Genetic polymorphisms in the IGFBP3 gene: Association with breast cancer risk and blood IGFBP-3 protein levels among Chinese women. Cancer Epidemiology Biomarkers and Prevention, 13(8), 1290–1295. https://doi.org/10.1158/1055-9965.1290.13.8
15. Rodriguez, S., Gaunt, T. R., & Day, I. N. M. (2009). Hardy-Weinberg equilibrium testing of biological ascertainment for Mendelian randomization studies. American Journal of Epidemiology, 169(4), 505–514.
16. Stiles, C. E., Hossain, B., & Drake, W. M. (2021). Acromegaly. Medicine, 49(8), 488–491.
17. Tang, W., Chen, S., Liu, J., Liu, C., Wang, Y., & Kang, M. (2019). Investigation of IGF1, IGF2BP2, and IGFBP3 variants with lymph node status and esophagogastric junction adenocarcinoma risk. Journal of Cellular Biochemistry, 120(4), 5510–5518. https://doi.org/10.1002/jcb.27834