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Research article

Relationship between CTLA4, TNF-α and PTPN22 gene polymorphism and the serum levels of antithyroglobulin and antiperoxidase antibodies in autoimmune thyroiditis

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Abstract: Autoimmune thyroiditis (AIT) is a chronic inflammatory that involves hyperactivation of the immune system against the thyroid gland, recognizing it as "nonself". The aim of this research was to identify the relationships between genetic polymorphism in *CTLA4*, *TNF-α* and *PTPN22* genes and the manifestation of AIT and levels of antithyroglobulin antibody (anti-TG Ab) and thyroid peroxidase antibody (anti-TPO Ab). The study was conducted during 2014–2020 and included 64 men and 106 women aged between 18 and 64 years with AIT. The control group consisted of 65 people (26 men, 39 women, aged between 20 and 65 years) without any thyroid pathologies or other autoimmune diseases. For molecular genetic analysis, real-time quantitative RT-PCR was used with fluorescently labeled FAM probes on a detection system CFX96 (BioRad). The results demonstrated that patients with the GG genotype and the G allele of the +49A/G polymorphism in the *CTLA4* gene have significantly higher titers of anti-TG Ab. High titers of anti-TG Ab were detected in 22.4% of patients with the GG genotype ($p = 0.005$, $\chi2 = 7.86$, OR = 0.237, 95% CI = 0.088–0.635), and in 55.6% of patients with the G allele ($p = 0.0012$, $\chi2 = 10.43$, OR = 0.360, 95%, CI = 0.192–0.674). At the same time, the A allele of the +49A/G polymorphism is significantly more common in patients with normal anti-TG Ab values—in 68.1% of individuals ($p = 0.0012$, $\chi2 = 10.43$, OR= 2.78, 95%, CI = 1.484–5.207). The results of the study indicate the prognostic significance of the G allele and the GG genotype of the +49A/G polymorphism of the *CTLA4* gene predicting the probability of occurrence of anti-TG and anti-TPO antibodies.

Keywords: autoimmune thyroiditis; CTLA4 gene; gene polymorphism; alleles; anti-TG Ab; anti-TPO Ab

1. Introduction

Autoimmune thyroiditis (AIT) is a chronic inflammatory disease occurring in the thyroid gland. The thyroid glands of AIT patients are characterized by diffuse lymphocytic infiltration, fibrosis, parenchymal atrophy and eosinophilic changes in some of the acinar cells [1–3]. There is a long-term destruction of the thyroid parenchyma, with a possible outcome in primary hypothyroidism [4,5]. Hashimoto's thyroiditis (HT) is an integral part of the spectrum of autoimmune diseases affecting the thyroid gland; it ranges from forms that usually do not require treatment (focal, silent and juvenile thyroiditis), to atrophic thyroiditis, manifested as hypothyroidism without goiter [6–8]. AIT occurs in 3–5% of the population [9–11], and the incidence of AIT is expected to increase in the future. This is associated with uncontrolled iodine intake and is expected to be 10–15 times more common in middle-aged women aged 30–50 years. Women suffer from AIT 4–8 times more often than men [12,13]. This difference is associated with the presence of the second X chromosome and the hormonal status of women. More often, the disease is detected in women over 60 years old; additionally, the frequency in the population is 6–11% [14,15].

2. Materials and methods

This study was conducted during the years of 2014–2020; 64 men and 106 women aged 18 to 64 years (totaling 170 patients with AIT were assessed). The control group consisted of 65 people aged 20 to 65 years and without any comorbidities, including no reported thyroid dysfunction or any other autoimmune diseases among which, 26 were men and 39 were women. The diagnosis of AIT was established on the basis of medical history, thyroid status, results of ultrasound examination of the thyroid gland and positive antibodies to the thyroid-stimulating hormone receptor (TSH). AIT patients were divided into two groups, where Group 1 consisted of 74 patients with a manifested form of the disease. The manifested form was defined on the basis of the clinical picture of the disease, i.e., the patient's complaints, increased TSH level and a decreased level of triiodothyronine (T3) and thyroxine (T4) hormones, as well as increased titers of antithyroglobulin antibody (anti-TG Ab) and thyroid peroxidase antibody (anti-TPO Ab). Group 2 consisted of 96 patients with a subclinical form of the disease. The diagnosis of the subclinical form of AIT was made on the basis of an increased level of TSH but normal levels of the hormones T3 and T4. Anti-TPO Ab and anti-TG Ab were determined by the immunochemiluminescent method by using an IMMULITE 2000 Xpi apparatus (USA). Medians and upper and lower quartiles were calculated to represent the quantitative parameters. Intergroup comparisons in terms of quantitative indicators were carried out by using the Mann-Whitney rank nonparametric test, taking into account the difference in the distribution of the analyzed indicators from the normal one.

Isolation of DNA from whole venous blood by using the DNA-EXPRESS-BLOOD reagent (SPF Litekh, Russia).

The collection of samples of peripheral venous blood was obtained from three institutions: The Therapeutic Clinic of the Azerbaijan Medical University, the Department of Biochemistry of the Azerbaijan Medical University and the YASHAM Medical Center (Baku).

Total genomic DNA was isolated via phenol-chloroform extraction. The choice of markers for analysis was determined by the gene-producing functions: transcription factors, cytokines and their receptors. Regarding the molecular genetic analysis for polymorphisms of the CTLA4, TNF-α and PTPN22 loci, real-time PCR was performed with fluorescently labeled probes on a CFX96 (Real-Time PCR Detection System) instrument (BioRad company, USA), followed by visualization and interpretation of the results in the Bio-Rad CFX96 program. It should be noted that the observed distribution of genotype frequencies for the studied locus of the studied genes in the control sample corresponded to the theoretically expected Hardy-Weinberg equilibrium distribution ($p = 0.76$). Statistical analysis was carried out by using the statistical software package Statistica 12 (USA).

2.1. Ethics approval of research

The present study was approved by the university ethics committee (Ref. no: AMU/ IEC/№12/ 07.02.2020).

3. Results

In patients with a manifested form of hypothyroidism, compared to the control group, the anti-TG Ab and anti-TPO Ab levels were significantly high, the median values of which were 470 (381–527) IU/ml and 530.5 (458–566) IU/ml, respectively (Table 1). In the case of the subclinical form of hypothyroidism, anti-TG Ab and anti-TPO Ab levels were significantly high ($p < 0.001$) as compared to the control group results. The median values of anti-TG Ab and anti-TPO Ab were 456 (394.5–543.5) IU/ml and 523 (464–568) IU/ml, respectively (Table 1).

Table 1. Anti-TG and anti-TPO antibodies in patients with various clinical forms of AIT Median (25–75%).

Laboratory parameters	Control group	AIT	
		Subclinical hypothyroidism	Manifest hypothyroidism
anti-TG Ab (IU/ml)	16 (13–30)	456* (394.5–543.5)	470* (381–527)
anti-TPO Ab (IU/ml)	20 (13–25)	523* (464–568)	530.5* (458–566)

Note: * $p < 0.001$ (compared to the control group).

The conducted studies showed significantly high titers of anti-TG Ab in patients with the GG genotype and the G allele of the +49A/G polymorphism of the CTLA4 gene. High titers of anti-TG Ab level were detected in 22.4% of patients with the GG genotype ($p = 0.005$, $\chi2 = 7.86$, OR = 0.237, 95% CI = 0.088–0.635), and in 55.6% of patients with the G allele ($p = 0.0012$, $\chi2 = 10.43$, OR = 0.360, 95% CI = 0.192–0.674). The A allele of the +49A/G polymorphism of the CTLA4 gene was significantly more common in patients with normal anti-TG Ab values; particularly, it was found in 68.1% of individuals ($p = 0.0012$, $\chi2 = 10.43$, OR = 2.78, 95% CI = 1.484–5.207), which corresponds to healthy individuals. In patients with AA and AG genotypes of the +49A/G gene polymorphism, the

normal titers of anti-TG Ab were observed in 31.9% and 63.8% of cases, as compared to patients with elevated antibody titers, which were observed in 26.3% and 51.3% of cases. But, the differences were not statistically significant (Table 2). According to polymorphisms 308A/G of the TNF-α gene and C1858T of the PTPN22 gene, there were no statistically significant differences in the titers of anti-TG Ab between the studied groups of patients, which indicates the absence of the influence of the 308A/G polymorphism of the TNF-α gene and C1858T polymorphism of the PTPN22 gene on the formation of antibodies to thyroglobulin.

Table 2. Distribution of allele and genotype frequencies by polymorphisms of the CTLA4, TNF-α and PTPN22 genes in patients with AIT by the level of anti-TG antibodies.

Alleles and genotypes	Patients with AIT n = 170 (Level of anti-TG Ab)				p	χ^2	OR	95% CI
	n	%	n	%				
	Up to 100 IU/ml n = 94		Higher than 100 IU/ml n = 76					
	polymorphism +49A/G of the CTLA4 gene							
AA	28	31.9	20	26.3	>0.05	-	-	-
AG	60	63.8	39	51.3	>0.05	-	-	-
GG	6	6.4	17	22.4	p = 0.005	7.86	0.237	0.088–0.635
A	64	68.1	33	43.4	p = 0.0012	10.43	2.780	1.484–5.207
G	30	31.9	43	56.6	p = 0.0012	10.43	0.360	0.192–0.674
	polymorphism 308A/G of the TNF-α gene							
AA	70	74.5	52	68.4	>0.05	-	-	-
AG	23	24.5	22	28.9	>0.05	-	-	-
GG	1	1.1	2	2.6	>0.05	-	-	-
A	76	80.1	58	76.3	>0.05	-	-	-
G	18	19.1	18	23.7	>0.05	-	-	-
	C1858T polymorphism of the PTPN22 gene							
CC	69	73.4	52	68.4	>0.05	-	-	-
CT	20	21.3	21	27.6	>0.05	-	-	-
TT	5	5.3	3	3.9	>0.05	-	-	-
C	71	75.5	54	71.1	>0.05	-	-	-
T	23	24.5	22	28.9	>0.05	-	-	-

Data on the distribution of allele and genotype frequencies by polymorphisms of the studied genes in the presence of antibodies to thyroperoxidase are presented in Table 3. As can be seen from the presented data, a high level of anti-TPO Ab (higher than 100 IU/ml) was observed in 22.7% of patients with the GG genotype and 50.0% with the G allele of the CTLA4 gene, which is significantly higher than the corresponding indicators in patients with normal values of anti-TPO Ab. The results indicate that the G allele and the GG genotype are risk markers for the synthesis of autoantibodies. On the contrary, for the A allele carriers (68.6%), low titers of anti-TPO Ab were found. For the AA and AG genotypes of the +49A/G polymorphism, no significant differences were found in the level of anti-

TPO Ab titers. There were no associations between the level of anti-TPO Ab and the genotypes and alleles of the 308A/G and C1858T polymorphisms of the TNF-α and PTPN22 genes.

Table 3. Distribution of allele and genotype frequencies according to polymorphisms of the CTLA4, TNF-α and PTPN22 genes in patients with AIT by the level of anti-TPO antibodies.

Alleles and genotypes	Patients with AIT n = 170 (Level of anti-TPO Ab)						p	χ^2	OR	95% CI
	n	%	n	%	n	%				
	Up to 35 IU/ml n = 67		35–100 UI/ml n = 59		Higher than 100 IU/ml n = 44					
	polymorphism +49A/G of the CTLA4 gene									
AA	25	37.3	19	32.2	12	27.3	>0.05	-	-	-
AG	34	50.7	24	40.7	22	50.0	>0.05	-	-	-
GG	8	11.9	16	27.1*	10	22.7*	0.030	4.69	0.364	0.143–0.928
A	46	68.6	31	52.5	22	50.0*	0.048	3.90	2.190	0.999–4.801
G	21	31.3	28	47.5	22	50.0*	0.048	3.90	0.457	0.208–1.001
	polymorphism 308A/G of the TNF-α gene									
AA	46	68.6	43	72.9	31	70.5	>0.05	-	-	-
AG	19	28.3	15	25.4	12	27.3	>0.05	-	-	-
GG	1	1.5	1	1.7	1	2.3	>0.05	-	-	-
A	56	83.6	51	86.4	36	81.8	>0.05	-	-	-
G	11	16.4	8	13.6	8	18.2	>0.05	-	-	-
	C1858T polymorphism of the PTPN22 gene									
CC	49	73.1	39	66.1	34	77.3	>0.05	-	-	-
CT	17	25.3	14	23.7	7	15.9	>0.05	-	-	-
TT	1	1.5	6	10.2*	3	6.8	>0.05	-	-	-
C	53	79.1	40	67.8	33	75.0	>0.05	-	-	-
T	14	20.9	19	32.2	11	25.0	>0.05	-	-	-

In case of manifested forms of AIT, 27% of patients were found to possess the GG genotype of the +49A/G polymorphism (rs231775) of the CTLA4 gene ($\chi2 = 5.84$, $p = 0.015$, OR = 3.06, 95% CI = 1.202–7.833). For other alleles and genotypes of the rs231775 polymorphism of the CTLA4 gene, no significant difference was found between the studied groups. The study of the frequency of distribution of alleles and genotypes of the 308A/G polymorphism of the TNF-α gene in patients with a manifested form of the disease showed a significant increase in the frequency of the GG, AG and allele G genotypes (Table 4). Thus, the GG genotype was detected in 16.2% of patients with a manifested form of AIT ($\chi2 = 4.83$, $p = 0.027$, OR = 4.0, 95% CI = 1.075–14.87); the AG genotype was detected in 56.8% of individuals with a manifested form of AIT and 30.7% of healthy individuals ($\chi2 = 9.458$, $p = 0.002$, OR = 2.95, 95% CI = 1.467–5.942). Allele G was also significantly more common in the manifested form of AIT (44.6%); in the control group, the frequency of this allele was 26.1% ($\chi2 = 5.109$, $p = 0.023$, OR = 2.27, 95% CI = 1.107–4.66). The AA genotype and the A allele

were protective against the development of overt AIT, and they were found in 27% and 55.4% of patients, respectively. There was no significant difference in the frequency of occurrence of genotypes and alleles of polymorphic markers C1858T of the PTPN22 gene between patients with a manifested form of AIT and healthy individuals.

Table 4. Distribution of frequencies of alleles and genotypes the CTLA4, TNF-α and PTPN22 genes polymorphism in manifested forms of AIT.

Alleles and genotypes	Patients with AIT with outcome in hypothyroidism n = 74		Control group n = 65		p	χ^2	OR	95% CI
	n	%	n	%				
polymorphism +49A/G of the CTLA4 gene								
AA	22	29.7	24	36.9	p = 0.36	0.808	0.722	0.355–1.46
AG	32	43.2	34	52.3	p = 0.285	1.14	0.69	0.355–1.357
GG	20	27.0	7	10.8	p = 0.015	5.84	3.06	1.202–7.833
A	38	51.4	43	66.1	p = 0.077	3.11	0.540	0.271–1.073
G	36	48.6	22	33.8	p = 0.077	3.11	1.85	0.931–3.680
polymorphism 308A/G of the TNF-α gene								
AA	20	27.0	42	64.6	p = 0.000	19.78	0.202	0.0985–0.417
AG	42	56.8	20	30.7	p = 0.002	4.58	2.95	1.467–5.942
GG	12	16.2	3	4.6	p = 0.027	4.83	4.0	1.075–14.87
A	41	55.4	48	73.8	p = 0.023	5.109	0.44	0.214–0.902
G	33	44.6	17	26.1	p = 0.023	5.109	2.27	1.107–4.66
C1858T polymorphism of the PTPN22 gene								
CC	52	70.3	49	75.4	p = 0.499	0.455	0.771	0.363–1.638
CT	20	27.0	14	21.5	p = 0.45	0.564	1.349	0.616–2.95
TT	2	2.7	2	3.1	p = 0.895	0.017	0.875	0.119–6.394
C	62	83.8	57	87.7	p = 0.512	0.429	0.725	0.265–1.901
T	12	16.2	8	12.3	p = 0.512	0.429	1.379	0.525–3.616

Many organ-specific autoimmune diseases are known to be associated with a genetic predisposition, which is partly determined by the polymorphism of two genes that regulate the function of T cells: CTLA4 and PTPN22 [16,17]. Perhaps, to some extent, their features determine the heterogeneity of autoimmune diseases. Both genetic and environmental factors play a role in the pathogenesis of autoimmune thyroid diseases (AITD) [18,19]. In order to identify the involvement of genetic factors in the etiology and pathogenesis of AITDs, as well as the influence of genetic factors on the biochemical parameters of patients with various clinical variants of the course of AIT, we studied the frequency of carriage of various genotypes and alleles of some genes; in particular, we studied the CTLA4, PTPN22 and TNF-α genes in patients with AIT and the effects of the genotypes of these genes on the levels of antibodies to TG (thyroglobulin) and TPO (thyroid peroxidase), which play an important role in the pathogenesis of AIT. It should be noted that the observed distribution of genotype frequencies for the studied locus of the studied genes in the control sample corresponded to

the theoretically expected Hardy-Weinberg equilibrium distribution (p = 0.76). Genetic predisposition plays a decisive role in the mechanisms of manifestation and progression of autoimmune inflammation in thyroiditis of autoimmune origin. We have studied the detection of the frequency of occurrence of genotypes and alleles of the CTLA4, PTPN22 and TNF-α genes in patients with AIT. As is known, the greatest contribution to the predisposition to AITDs belongs to the IDDM1 locus, which contains the genes of the major histocompatibility complex HLA class II [20,21]. The pathology of AIT depends on differences in the ethnicity and differences in the inclusion criteria in the study groups. In addition, multifactorial diseases, which include AIT, are characterized by the realization of a genetic predisposition to the disease only in the presence of certain combinations of genotypes and alleles and triggering environmental factors. The results of the distribution of allele and genotype frequencies of the CTLA4, PTPN22, and TNF-α genes in patients with a manifested form of the disease showed a statistically significant increase in the frequency of the GG genotype of the +49A/G (rs231775) polymorphism of the CTLA4 gene, which was observed in 27% of patients with a manifested form of the disease. The 308A/G polymorphism of the TNF-α gene in the manifested form of the disease was characterized by a significant increase in the frequency of the GG genotype and AG and G alleles. Thus, the GG genotype was detected in 16.2% of patients with a manifested form of AIT, and in 4.6% of the control group ($\chi2 = 4.83$, p = 0.027, OR = 4.0, 95% CI = 1.075–14.87); the AG genotype was detected in 56.8% of individuals with a manifested form of AIT, and in 30.7% of healthy individuals ($\chi2 = 9.458$, p = 0.002, OR = 2.95, 95% CI = 1.467–5.942). The G allele was also significantly more common in the manifested form of AIT (44.6%); in the control group, the frequency of this allele was 26.1% ($\chi2 = 5.109$, p = 0.023, OR = 2.27, 95% CI = 1.107–4.66).

The study indicated a significant relationship between the G allele and the GG and AG genotypes of the 308A/G polymorphism of the TNF-α gene in individuals with AIT. This is consistent with studies by a number of authors who have identified a link between these markers and Graves' disease, which indicates that this allele may play a role in the pathogenesis of AIT. But, the literature also found conflicting data on the genotype and allele frequencies of the 308A/G TNF-α polymorphism in HT. TNF-α 308A/G polymorphisms have been reported to be associated with Graves' disease in Caucasians, but not in Asians [20].

The PTPN22 gene is located on the short arm of chromosome 1 (1p13) and encodes two isoforms of cytoplasmic enzymes: LYP1 and LYP2. These proteins contain an N-terminal catalytic domain, and the amino acid sequence outside of the catalytic domain determines their intracellular position. It is hypothesized that such a mutation in PTPN22 may predispose an individual to autoimmune diseases by failing to delete autoreactive T cells, or by reducing the activity of T suppressors. The 1858 C/T polymorphism of the PTPN22 gene, in many populations, is associated with an increased risk of developing autoimmune diseases, such as type 1 diabetes mellitus, rheumatoid arthritis and systemic lupus erythematosus [20–24]. The presented literature data on the study of the relationship between the 1858 C/T polymorphism of the PTPN22 gene and the development of thyroid disease differ in different populations. A number of studies have shown that, when examining 166 patients with Graves' disease and 154 people in a control group without a thyroid disease, no significant difference was found in the frequency of genotypes and alleles of the C1858T polymorphism of the PTPN22 gene [24]. Other studies have confirmed the association of the above polymorphism with a predisposition to Graves' disease. In a UK study of 549 patients with Graves' disease and 429 apparently healthy individuals, it was found that the frequency of the T-allele was set at 13.8% (151 out of 1098 alleles) of cases in patients with Graves' disease, and only in 7.8% in healthy individuals

(67 of 858 alleles) (OR = 1.88; 5–95% CI = 1.39–2.55) [25]. The main biochemical characteristic of AIT is the presence of thyroid autoantibodies against the two main thyroid antigens TPO (thyroid peroxidase) and TG (thyroglobulin). The TPO antigen, located on the apical membrane of the thyrocyte, is necessary for the synthesis of thyroid hormones, catalysis of iodine oxidation, iodination of tyrosine residues and binding of iodotyrosines to T3 and T4. Antibodies against TPO and TG belong to the class of immunoglobulin G, and both have a high affinity for their respective antigens. Anti-TG Ab and anti-TPO Ab can activate complementary reactions and cause damage to thyroid cells due to antibody-dependent cell cytotoxicity. T-cell mediated cytotoxicity and the activation of apoptosis pathways are known to influence disease outcome. However, TG antibodies constitute a significant marker for diagnosing thyroid autoimmunity. But, in individuals with HT, TPO Ab is present in almost all (>90%) patients, while TG Ab can be detected in about 80%.

The genes we have studied regulate the functioning of T cells, and they affect B cells, which produce anti-TG and anti-TPO Ab. Therefore, it seems important to study the levels of the above antibodies for different genotypes of the studied polymorphic markers. The obtained data demonstrated significantly high levels of anti-TG antibodies in patients with the GG genotype and the G allele of the +49A/G polymorphism of the CTLA4 gene. The A allele of the +49A/G polymorphism of the CTLA4 gene was significantly more common in patients with normal TG Ab values, i.e., in 68.1% of individuals ($p = 0.0012$, $\chi 2 = 10.43$, OR = 2.78, 95%, CI = 1.484–5.207). The data revealed that 308A/G polymorphisms of the TNF-α gene and C1858T of the PTPN22 gene had no statistically significant differences in antibody titers to thyroglobulin between the studied groups of patients, which indicates the absence of an effect of the 308A/G polymorphism of the TNF-α gene and the C1858T polymorphism of the PTPN22 gene on the formation of antibodies to thyroglobulin. The activity of the autoimmune process in the thyroid gland was assessed by the levels of antibodies to TPO in the blood serum. In the present study, the patient results for the G allele and the homozygous GG genotype of the +49A/G polymorphism of the CTLA4 gene showed elevated titers of antibodies to TPO. On the contrary, allele A carriers were found to have significantly low titers of TPO Ab. There were no associations between the titer of anti-TPO Ab and the genotypes and alleles of the 308A/G and C1858T polymorphisms of the TNF-α and PTPN22 genes, respectively.

4. Conclusions

The GG genotype and the G allele of the +49A/G polymorphism of the CTLA4 gene are also risk markers for the synthesis of autoantibodies to TPO. In patients with the G allele and the homozygous GG genotype of the +49A/G polymorphism of the CTLA4 gene, the titer of antibodies to TPO was significantly increased; and, the A allele of this polymorphism was found to be protective against anti-TPO Ab. It should be noted that the revealed frequency of occurrence of the polymorphic genotypes and alleles of the studied genes, as well as the observed titer of anti-TG and anti-TPO Ab, was established for all patients with AIT, including the patients with both a manifested form of the disease and the subclinical form of AIT. The results of the study indicate the prognostic significance of the G allele and the GG genotype of the +49A/G polymorphism of the CTLA4 gene redicting the probability of occurrence of anti-TG and anti-TPO antibodies. One potential limitation of our research is that the study was regional. Since the results of such studies depend on genetic and ethnic differences, further studies from multiple regions should be conducted to understand the correlation between the results of genetic analyses and manifestations of AIT.

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Conflict of interest

The authors declare no conflict of interest.

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