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Cytokine Gene Polymorphisms in Common Variable Immunodeficiency

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Key Words
Common variable immunodeficiency · Cytokine · Genetic polymorphism · Interleukin-2 · Transforming growth factor-β

Abstract
Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, characterized by hypogammaglobulinemia and an increased susceptibility to recurrent infections, autoimmunity and cancers. There are some conflicting results regarding the cytokine profile of CVID patients. While cytokine production could be associated with gene polymorphism, genetic profiles of a number of cytokines were analyzed in this study. The allele and genotype frequencies of the polymorphic genes coding for interleukin (IL)-2, IL-12, interferon-γ and transforming growth factor (TGF)-β were investigated in 30 patients with CVID in comparison with 140 controls. The genotype TGF-β CG at position +915 was significantly overrepresented in the patient group, while the frequencies of the genotypes TGF-β TT at +869 and GG at +915 were significantly decreased in the patient group in comparison with controls. TGF-β TC and IL-2 GT were the most frequent haplotypes in the patients, whereas the TGF-β TG haplotype was significantly decreased in the patient group. The allele and genotype frequencies of interferon-γ at position UTR +5644 and also IL-12 at position –1188 were similar in patients and controls. Cytokine single nucleotide polymorphisms could play a role in the pathophysiology of CVID. Considering the significantly lower frequency of the high production haplotype (TG) and the higher frequency of the low production halplotype (TC) of TGF-β, low production of this cytokine is expected in some CVID patients.

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of predominantly antibody deficiencies, characterized by hypogammaglobulinemia and increased susceptibility to recurrent pyogenic infections, autoimmune disorders and malignancies [1–6]. CVID is the most common symptomatic primary immunodeficiency disease [7].

Although the pathogenesis of CVID is not fully understood [8, 9], a defect in B cell differentiation, as well as several abnormalities of T cells and dendritic cells in some patients have been reported [10–16], and attempts to identify the underlying immune system defects are still continued. Recent investigations to identify the genes responsible for CVID have resulted in findings of some new monogenic defects [9] like ICOS deficiency [17],

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CD19 deficiency [18] and, possibly, TACI deficiency [19, 20].

Cytokines play an essential role in antibody synthesis. Although the cytokine production in CVID has been evaluated in several studies, conflicting results were found [21–24]. The expression and secretion of cytokines could be affected, at least in part, by genetic polymorphisms within coding and promoter regions of cytokine genes [25, 26]. Considering the cytokine variation in CVID and the important role of cytokine single nucleotide polymorphisms in the susceptibility to several diseases [27–29], it is noteworthy to conduct such a study in CVID.

This study was performed in patients with CVID for the first time to analyze the genotype frequencies of a number of polymorphic genes coding for cytokines in this group of patients.

Materials and Methods

Subjects

Thirty selected unrelated patients with CVID (18 males and 12 females) who were referred to the Department of Pediatrics of Children's Medical Center Hospital, Tehran, Iran, during the year 2007, were investigated. The patients were diagnosed based on international criteria, including decreased serum levels of at least 2 immunoglobulins (IgG, IgA and IgM) by 2 standard deviations from normal mean values for age, and genetic exclusion of other well-defined antibody deficiencies [9, 30]. Patients <2 years of age were excluded because of the possibility of transient hypogammaglobulinemia of infancy. The patient characteristics, which have been explained previously [31], are briefly presented in table 1.

One hundred and forty healthy control subjects were also selected from blood donors at Iranian blood transfusion organizations in Tehran [32]. All control subjects were healthy, unrelated and randomly selected from this region.

Our project was approved by the Ethical Committee of Tehran University of Medical Sciences. Written informed consent was obtained from all subjects before sampling.

Genotyping

After DNA extraction from whole blood, using the salting out method, cytokine typing was performed by the polymerase chain reaction with sequence-specific primer assay (PCR-SSP kit, Heidelberg University, Heidelberg, Germany) [32]. Amplification was carried out using a thermal cycler Techne Flexigene apparatus (Rosche, Cambridge, UK) under the following conditions: initial denaturation at 94°C for 2 min; denaturation at 94°C for 10 s; annealing and extension at 65°C for 1 min (10 cycles); denaturation at 94°C for 10 s; annealing at 61°C for 50 s; extension at 72°C for 30 s (20 cycles). The presence or absence of polymerase chain reaction products was visualized by 2% agarose gel electrophoresis. When the quality of the agarose gel was not acceptable, the result was excluded. After electrophoresis, the gel was placed on a UV transilluminator, and a picture for interpretation and documentation was taken. Each of the primer mixes contained a control primer pair that amplified either a part of the β-globin gene or a part of the C-reactive protein gene. The β-globin control primers produce a 89-bp fragment, while the primer pairs amplifying the C-reactive protein gene produced a 440-bp amplicon. The allele and genotype frequencies of the following cytokine genes were determined: transforming growth factor (TGF)-β, T(+869)C and G(+915)C; interleukin (IL)-2, G(–330)T and G(+166)T; IL-12, C(–1188)A; and interferon (IFN)-γ, A(UTR +5644)T.

Statistics

Allele frequencies were estimated by direct gene counting. Allele frequencies of various genotypes were compared using the χ^2 test. The odds ratios and 95% confidence intervals were calculated for each allele/genotype/haplotype in the patient and control groups. A p value <0.05 was considered significant for alleles. In order to adjust multiple comparisons, the Bonferroni correction method was utilized in computing of confidence intervals and rejection of tests at the 0.05 level. Thus, the resulted p value is significant for less than $\alpha/2m$ (0.008 for genotypes and 0.006 for haplotypes).

Results

The frequencies of the following alleles in the patient group were significantly higher than in the control group: TGF-β C allele at position +915 (45% in patients vs. 8% in controls; $p < 0.001$) and IL-2 T allele at position +166 (39% in patients vs. 21% in controls; $p = 0.007$) (table 2).

The frequency of the TGF-β CG genotype at position +915 in the patient group was significantly higher than in controls (83% in patients vs. 12% in controls; $p < 0.001$), whereas the frequencies of the genotypes TGF-β TT at position +869 (0% in patients vs. 20% in controls; $p = 0.005$) and GG at position +915 (13% in patients vs. 86% in controls; $p < 0.001$) were significantly decreased in the patient group in comparison with controls (table 3).

The most frequent haplotypes in the patients were TGF-β TC (33% in patients vs. 0% in controls; $p < 0.001$) and IL-2 GT (16% in patients vs. 0.3% in controls; $p < 0.001$). The frequency of TGF-β TG in the patients was significantly lower than in controls (12% in patients vs. 53% in controls; $p < 0.001$) (table 4). TGF-β CG/TC (+869, +915) was the most common genotype (66.7%) in the patient group, while no control subject had such a genotype ($p < 0.001$). IL-2 TG/GT (–330, +166) was also one of the most common genotypes (26.7%), which was significantly overrepresented in comparison with controls ($p < 0.001$).

Table 1. Characteristics of the CVID patients

Patient No.	Sex	Current age years	IgG mg/dl	IgM mg/dl	IgA mg/dl	Clinical manifestations	Other findings
1	female	18	390	50	75	multi-organ recurrent infections + autoimmunity + malignancy	splenomegaly, lymphadenopathy, bronchiectasis
2	female	20	500	10	45	multi-organ recurrent infections + autoimmunity	splenomegaly, lymphadenopathy, bronchiectasis
3	male	13	470	45	35	multi-organ recurrent infections + autoimmunity	splenomegaly, lymphadenopathy, bronchiectasis
4	male	14	340	20	10	multi-organ recurrent infections + autoimmunity	splenomegaly, bronchiectasis
5	male	10	140	15	15	multi-organ recurrent infections + autoimmunity	splenomegaly, bronchiectasis
6	male	9	320	15	55	multi-organ recurrent infections + autoimmunity	splenomegaly, bronchiectasis
7	male	9	380	50	5	multi-organ recurrent infections + autoimmunity	bronchiectasis
8	male	13	255	50	70	multi-organ recurrent infections + autoimmunity	–
9	female	9	<50	30	<5	multi-organ recurrent infections	splenomegaly, bronchiectasis
10	male	16	80	5	5	multi-organ recurrent infections	splenomegaly, bronchiectasis
11	male	16	105	30	30	multi-organ recurrent infections	splenomegaly, bronchiectasis
12	male	21	130	60	10	multi-organ recurrent infections	splenomegaly, lymphadenopathy
13	male	17	90	90	10	multi-organ recurrent infections	splenomegaly, lymphadenopathy
14	female	12	350	35	<5	recurrent respiratory infections	splenomegaly, lymphadenopathy
15	male	47	<50	25	<5	multi-organ recurrent infections	lymphadenopathy, bronchiectasis
16	female	22	355	<10	15	multi-organ recurrent infections	lymphadenopathy, bronchiectasis
17	female	13	115	30	50	multi-organ recurrent infections	lymphadenopathy
18	male	50	250	<10	<5	multi-organ recurrent infections	bronchiectasis
19	male	20	<50	30	<5	multi-organ recurrent infections	bronchiectasis
20	female	20	220	15	10	multi-organ recurrent infections	bronchiectasis
21	male	25	80	10	20	multi-organ recurrent infections	–
22	female	23	250	50	35	multi-organ recurrent infections	–
23	male	12	310	50	10	multi-organ recurrent infections	–
24	female	11	<50	40	<5	multi-organ recurrent infections	–
25	male	10	<50	20	5	multi-organ recurrent infections	–
26	male	5	120	<10	220	multi-organ recurrent infections	–
27	male	4	90	30	90	multi-organ recurrent infections	–
28	female	21	290	30	<5	recurrent respiratory infections	bronchiectasis
29	female	8	80	15	5	recurrent respiratory infections	splenomegaly
30	female	9	100	10	5	recurrent respiratory infections	–

The association of a specific genotype/haplotype with the severity of disease was also analyzed; however, there was no significant association between different genotypes/haplotypes and the presence of clinical phenotypes such as splenomegaly, lymphadenopathy, bronchiectasis and autoimmunity.

Discussion

There are several studies indicating cytokine production abnormalities in CVID [21–24]. While cytokine production could be affected by cytokine gene polymorphism, we have genotyped a sample of CVID patients for a number of these cytokines.

TGF-β is a multifunctional cytokine, which has both stimulatory and inhibitory effects on different cell types [33]. A significant negative association with the TGF-β TT (+869) and TGF-β GG (+915) genotypes was shown in CVID patients, whereas TGF-β CG at +915 was significantly overrepresented. Although the C allele at +915 is a rare allele in different ethnic groups, approximately half of the patients have this allele, which is significantly higher than in the normal population [32]. Considering the significantly lower frequency of the high production haplotype (TG) and the higher frequency of the low pro-

Table 2. Allele frequencies of CVID patients in comparison with normal controls

Cytokine	Position	Allele	Patients (n = 30)	Controls (n = 140)	p value	Odds ratio
TGF-β	+869	C	33 (55.0)	131 (47.5)	0.359	1.35 [0.77–2.37]
		T	27 (45.0)	145 (52.5)		0.74 [0.42–1.29]
TGF-β	+915	C	27 (45.0)	21 (7.6)	<0.001	9.94 [5.06–19.53]
		G	33 (55.0)	255 (92.4)		0.1 [0.05–0.2]
IL-2	+166	G	34 (60.7)	219 (78.8)	0.007	0.42 [0.23–0.77]
		T	22 (39.3)	59 (21.2)		2.40 [1.31–4.41]
IL-2	–330	G	26 (46.4)	110 (39.6)	0.421	1.32 [0.74–2.36]
		T	30 (53.6)	168 (60.4)		0.76 [0.42–1.35]
IFN-γ	UTR +5644	A	36 (60.0)	140 (50.7)	0.246	1.46 [0.83–2.57]
		T	24 (40.0)	136 (49.3)		0.69 [0.39–1.21]
IL-12	–1188	A	40 (69.0)	204 (72.9)	0.659	0.83 [0.45–1.53]
		C	18 (31.0)	76 (27.1)		1.21 [0.65–2.24]

Figures in parentheses are percentages; figures in brackets indicate 95% confidence intervals.

Table 3. Genotype frequencies of CVID patients in comparison with normal controls

Cytokine	Position	Genotypes	Patients (n = 30)	Controls (n = 140)	p value	Odds ratio
TGF-β	+869	CC	3 (10.0)	20 (14.5)	0.77	0.66 [0.14–3.16]
		CT	27 (90.0)	91 (65.9)	0.014	4.65 [1.04–20.9]
		TT	0 (0.0)	27 (19.6)	0.005[1]	0 [0.0–1.48]
TGF-β	+915	CC	1 (3.3)	2 (1.5)	0.448	2.34 [0.12–44.7]
		CG	25 (83.3)	17 (12.3)	<0.001[1]	35.59 [9.39–134]
		GG	4 (13.3)	119 (86.2)	<0.001[1]	0.02 [0.0–0.08]
IL-2	+166	GG	9 (32.1)	82 (59.0)	0.017	0.33 [0.12–0.94]
		GT	16 (57.1)	55 (39.6)	0.132	2.04 [0.75–5.53]
		TT	3 (10.7)	2 (1.4)	0.034	8.22 [0.88–77.5]
–	–330	GG	1 (3.6)	8 (5.8)	0.993	0.61 [0.05–8.0]
		GT	24 (85.7)	94 (67.6)	0.091	2.87 [0.73–11.1]
		TT	3 (10.7)	37 (26.6)	0.12	0.33 [0.07–1.51]
IFN-γ	UTR +5644	AA	10 (33.3)	43 (31.2)	0.988	1.11 [0.41–3.0]
		AT	16 (53.3)	54 (39.1)	0.22	1.78 [0.69–4.62]
		TT	4 (13.3)	41 (29.7)	0.108	0.36 [0.09–1.4]
IL-12	–1188	AA	14 (48.3)	72 (51.4)	0.916	0.88 [0.33–2.34]
		CA	12 (41.4)	60 (42.9)	0.884	0.94 [0.35–2.51]
		CC	3 (10.3)	8 (5.7)	0.404	1.9 [0.35–10.3]

Figures in parentheses are percentages; figures in brackets indicate 95% confidence intervals.
[1] Significant at the 5% level adjusted for Bonferroni multiple comparison correction.

duction halplotype (TC), a low production of TGF-β is expected in CVID patients [25]. TGF-β seems to be important in IgA class switching [34], and there are some evidences that T cells from CVID patients secrete less TGF-β than healthy controls [35]. While impaired somatic hypermutation was described in a group of patients with CVID [36], some cytokines such as TGF-β have an important role in the activation and nuclear translocation of specific nuclear factors, which activate the CH promoter of specific heavy-chain CH genes for transcription [20].

IL-2 is a Th1 cytokine which plays an important role in the proliferation of activated T cells and induces the production of suppressive T cells to terminate lympho-

Table 4. Haplotype frequencies of CVID patients in comparison with normal controls

Cytokine	Haplotype	Patients (n = 30)	Controls (n = 140)	p value	Odds ratio
TGF-β (+869, +915)	CG	27 (45.0)	110 (39.9)	0.555	1.24 [0.61–2.48]
	TG	7 (11.7)	145 (52.5)	<0.001[1]	0.12 [0.04–0.34]
	CC	6 (10.0)	21 (7.6)	0.599	1.35 [0.40–4.57]
	TC	20 (33.3)	0 (0.0)	<0.001[1]	–
IL-2 (–330, +166)	GG	16 (28.6)	107 (38.8)	0.197	0.63 [0.28–1.40]
	TG	18 (32.1)	112 (40.6)	0.303	0.69 [0.31–1.54]
	TT	13 (23.2)	56 (20.3)	0.756	1.19 [0.50–2.83]
	GT	9 (16.1)	1 (0.3)	<0.001[1]	52.66 [3.67–749.95]

Figures in parentheses are percentages; figures in brackets indicate 95% confidence intervals.
[1] Significant at the 5% level adjusted for Bonferroni multiple comparison correction.

cyte response [37]. Two single base substitutions have been identified at positions –330 (G/T) and +166 (G/T) relative to the transcription start point [38]. In our study, there was no significant difference in genotype frequencies between patient and control groups, while IL-2 TG/GT (–330, +166) was one of the most common genotypes that was significantly overrepresented in the patient group.

IFN-γ is a Th1 cytokine which plays an essential role in the defense against viruses and intracellular agents. The allele and genotype frequencies of IFN-γ at position UTR +5644 were similar in the patients and controls. Although a recent study by Pons et al. [23] showed a insignificantly higher production of IL-2 and IFN-γ after T-cell stimulation, in our recent study and also in the study by Inoue et al. [39], there was no significant difference in the production of these cytokines between patient and control groups. A granulomatous condition, which could lead to a trend to Th1 response, was not detected in our patient group. Thus, Th1 function seems to be normal, at least in a part of CVID patients [24, 39].

IL-12 is an immunomodulatory cytokine, produced by macrophages and dendritic cells, which plays an important role in polarizing T cells into Th1 response [40, 41]. The allele and genotype frequencies of IL-12 at position –1188 were similar in patients and controls. In a study on dendritic cells cultured in the presence of CVID patient sera, there was no significant difference in the production of IL-12 between patients and controls [42].

In conclusion, while the low frequency of TGF-β TG (high production) and the high frequency of TGF-β TC (low production) haplotypes have been demonstrated in this study, the low production of TGF-β remains a speculation. No difference in IFN-γ and IL-12 gene polymorphisms could support the concept of normal Th1 type responses, at least in part of CVID patients. Further studies on the associations between cytokine gene polymorphisms and immunological phenomena may provide a satisfactory explanation for the pathophysiology of the disease.

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