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ORIGINAL ARTICLE

Mannose-binding lectin polymorphisms in common variable immunodeficiency

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Abstract Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, characterized by hypogammaglobulinemia and increased susceptibility to infections, autoimmunity and malignancies. This study was performed to analyze the Mannose-binding lectin (MBL) polymorphisms in Iranian patients with CVID. Thirty-five CVID patients who were treated at Children's Medical Center and 100 matched controls were enrolled in this study. Sixth single-nucleotide polymorphisms of the MBL gene were analyzed using PCR–SSP method. Comparison of MBL exon 1 coding alleles between patients and controls revealed that A allele (wild-type) was significantly decreased in CVID group, whereas B allele was overrepresented in the patient group. High frequency of heterozygous (A/O) in the patient group and high frequency of homozygous for wild-type coding regions in the control group were detected. Comparison of MBL haplotype promoters between CVID patients and controls showed that LYPB haplotype was significantly overrepresented in the CVID group. Mutant and low-producing MBL alleles and haplotypes might reflect as an associated genetic factor in CVID patients, which could play as a susceptibility factor in CVID.

Keywords Mannose-binding lectin · Polymorphisms · Common variable immunodeficiency

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Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of disorders, characterized by hypogammaglobulinemia and an increased susceptibility to recurrent and chronic infections [1, 2]. The clinical spectrum of CVID is broad and a number of patients also suffer from autoimmune disorders and cancers [2–5].

Despite several years of investigations on the nature of defect(s) in CVID, the basic molecular defect in CVID is still unknown. Most of the patients have normal number of peripheral T and B lymphocytes. The defects of molecules regulating activation and terminal differentiation of B lymphocytes have been described in some patients with CVID. The core defect is in late B cell differentiation, leading to defective immunoglobulin production, while some patients can have abnormal response to both protein and polysaccharide antigens [6–12]. Other components of the immune system such as T cells [13–17] and dendritic cells [18–22] could also be involved in CVID patients.

The complement system, including mannose-binding lectin (MBL) pathway represents an important component of the innate immune system. MBL belongs to collectins protein family, which have collagen-like and lectin domains. The major functions of serum MBL are

complement activation, opsonophagocytosis, recognition of altered self structures, and modulation of the inflammation. Dysregulation in this system could be associated with both increased susceptibility to infections and autoimmune diseases [23–25]. Some documented studies [26–38] showed that dysregulation of MBL pathway, caused structural mutations of the *MBL2* gene [26] and three different structural variants, including B, C, D and the promoter haplotypes HY (high producing), LY (intermediate) and LX (low producing) have the most important effects on serum MBL concentration. MBL variants and polymorphisms [27, 28], is associated with an increased frequency of severe respiratory tract infections, autoimmunity and earlier onset age of disease in CVID. The aim of this study was to analyze the MBL polymorphisms in Iranian patients with CVID.

Methods

Patients and controls

In this study, 35 diagnosed patients with CVID who were treated at Children's Medical Center Hospital, Iran were selected as patient group. One hundred sex and age-matched healthy control subjects were also enrolled in this study. All the patients and control were recruited from Tehran, the capital of Iran. The diagnosis of CVID was made according to the diagnostic criteria for CVID [29, 30], including the reduction of at least two serum immunoglobulin isotypes (serum IgG, IgA and IgM) by more than two standard deviations from normal mean values for age. Other well-defined immunodeficiencies such as X-linked agammaglobulinemia was excluded by molecular studies in the patients with X-linked pattern of inheritance and very low numbers of circulating B cells [31]. We excluded patients <2 years of age, because of the possible diagnosis of transient hypogammaglobulinemia.

SNP genotyping

Sixth SNPs of the MBL gene, including: two at promoter (−550, −221), one at 5′ untranslated region (UTR) and others at exon 1 (Codons 52, 54, 57) were analyzed in the participants of this study.

Genotyping was performed using polymerase chain reaction (PCR) with sequence-specific primers (PCR–SSP). In brief, genomic DNA (200 ηg) was amplified with 0.2 mM dNTPs and 20 ρmol of each specific primer, in a buffer containing 10 mM Tris–HCl (pH 8.3), 50 mM KCl, 0.01% (w/v) gelatin and 1 U of *Taq* polymerase (Roche, Basel, Switzerland) in a final volume of 20 µl. The final concentration of the control primers and the $MgCl_2$ was different in different mixes.

Thermal cycling conditions for exon 1 gene amplification were as follows: 95°C for 10 min, followed by 30 cycles of 94°C for 20 s, 62°C for 20 s, 72°C for 30 s and 72°C for 5 min. Thermal cycling conditions for promoter gene amplification were as follows: 95°C for 10 min, followed by 30 cycles of 94°C for 30 s, 59°C for 30 s and 72°C for 45 s. Thermal cycling conditions for 5′ UT amplification were as follows: 95°C for 10 min, followed by 30 cycles of 94°C for 30 s, 66°C for 30 s, 72°C for 45 s.

The list of assay primers is shown in the Table 1. The genotypes were determined by the presence or absence of a band after electrophoresis in a 2% agarose gel stained with ethidium bromide, visualized by ultraviolet light and photographically recorded.

Statistical analysis

Allele and genotype frequencies were calculated by direct counting. Differences in MBL allele and genotype frequencies among CVID patients and healthy controls were determined using chi-square statistics. The odds ratio (OR) and 95% confidence interval (CI) were also calculated. A probability value of <0.05 was considered statistically significant in all analyses.

Results

Characteristics of the patients

In this study, 35 patients with CVID (20 male and 15 female), with age range of 5–48 years (median 14, mean 17.63 ± 10.71 years), were investigated. The first manifestation of disease occurred at a median age of 11 months (range 1–409), while the median age of patients at the time of diagnosis was 79 months (range 26–516) months. All of the patients experienced recurrent infections during the course of disease. Sixteen cases developed bronchiectasis due to recurrent pneumonia. Splenomegaly and autoimmunity were detected in 15 and 11 cases, respectively.

MBL exon 1 alleles

Comparison of MBL exon 1 coding alleles between CVID patients and controls revealed that A allele was significantly decreased in the CVID group ($P = 0.047$, OR 0.54, 95% CI 0.30–0.99), whereas B allele was overrepresented in the group of patients ($P = 0.012$, OR 2.32, 95% CI 1.18–4.55). There was no significant difference in C and D alleles between two studied groups (Table 2).

Table 1 PCR primers for MBL genotyping

SNP position	Forward	Reverse
Exon 1 Codon 52 (+223) D	5′-CTGCACCCAGATTGTAGGACAGAG-3′	5′-TCTCCCTTGGTGCCATCACA-3′
Exon 1 Codon 52 (+223) non D	5′-CTGCACCCAGATTGTAGGACAGAG-3′	5′-TCTCCCTTGGTGCCATCACG-3′
Exon 1 Codon 54 (+230) B	5′-CTGCACCCAGATTGTAGGACAGAG-3′	5′-CCCCCTTTTCTCCCTTGGTGT-3′
Exon 1 Codon 54 (+230) non B	5′-CTGCACCCAGATTGTAGGACAGAG-3′	5′-CCCCCTTTTCTCCCTTGGTGC-3′
Exon 1 Codon 57 (+239) C	5′-CTGCACCCAGATTGTAGGACAGAG-3′	5′-ACGTACCTGGTTCCCCCTTTTCTT-3′
Exon 1 Codon 57 (+239) non C	5′-CTGCACCCAGATTGTAGGACAGAG-3′	5′-ACGTACCTGGTTCCCCCTTTTCTC-3′
Exon 1 Control	5′-TGCCTTCCCAACCATTCCCTTA-3′	5′-CCACTCACGGATTTCTGTTGTGTTTC-3′
Promoter H (-550)	5′-GCTTACCCAGGCAAGCCTGTG-3′	5′-AACAAATGGGACCGTGCATTGC-3′
Promoter L (-550)	5′-GCTTACCCAGGCAAGCCTGTC-3′	5′-AACAAATGGGACCGTGCATTGC-3′
Promoter Y (-221)	5′-CCTGCCAGAAAGTAGAGAGG-3′	5′-CTGGAAGACTATAAACATGCTTTCC-3′
Promoter X (-221)	5′-CCTGCCAGAAAGTAGAGAGG-3′	5′-GGAAGACTATAAACATGCTTTCG-3′
5′UT P (+4)	5′-CAGATTGTAGGACAGAGGGCATGCTC-3′	5′-CCAGGCAGTTTCCTCTGGAAGG-3′
5′UT Q (+4)	5′-TTGTAGGACAGAGGGCATGCTT-3′	5’-CCAGGCAGTTTCCTCTGGAAGG-3′

Table 2 Mannose-binding lectin exon 1 allele frequencies in CVID patients and controls

Allele	CVID ($n = 35$) Number (%)	Controls ($n = 100$) Number (%)	P value	Odds ratio (95% confidence interval)
A	40 (57.2)	142 (71)	0.047*	0.54 (0.30–0.99)
B	22 (31.4)	33 (16.5)	0.012*	2.32 (1.18–4.55)
C	4 (5.7)	5 (2.5)	0.366	2.36 (0.51–10.52)
D	4 (5.7)	20 (10)	0.400	0.55 (0.15–1.77)

* Yates corrected

MBL exon 1 genotypes

Comparison of MBL exon 1 coding genotypes between CVID patients and controls indicated high frequency of heterozygous (A/O) in the patient group ($P = 0.016$, OR 2.89, 95% CI 0.30–0.99). However, more controls were homozygous for wild-type coding regions ($P = 0.009$, OR 0.30, 95% CI 0.11–0.77) (Table 3).

MBL promoter haplotype

Comparison of MBL haplotype promoters between patient group and control group showed that LYPB haplotype was significantly overrepresented in CVID group ($P = 0.009$, OR 2.41, 95% CI 1.22–4.73). There was not any significant difference in other haplotypes between two studied groups (Table 4).

Table 3 Mannose-binding lectin exon 1 genotype frequencies in CVID patients and controls

Genotype	CVID ($n = 35$) Number (%)	Controls ($n = 100$) Number (%)	P value	Odds ratio (95% confidence interval)
A/A	8 (22.9)	50 (50)	0.009*	0.30 (0.11–0.77)
A/O	24 (68.6)	43 (43)	0.016*	2.89 (1.19–7.11)
O/O	3 (8.6)	7 (7)	0.94	1.25 (0.24–5.82)

* Yates corrected

Table 4 Mannose-binding lectin promoter haplotype frequencies in CVID patients and controls

Haplotype	CVID ($n = 35$) Number (%)	Controls ($n = 100$) Number (%)	P value	Odds ratio (95% confidence interval)
HYPA	22 (31.4)	69 (34.5)	0.74	0.87 (0.47–1.62)
LYPB	22 (31.4)	32 (16)	0.009*	2.41 (1.22–4.73)
LYQA	12 (17.2)	46 (23)	0.39	0.69 (0.32–1.47)
LXPA	5 (7.2)	24 (12)	0.36	0.56 (0.18–1.65)
HYPD	4 (5.7)	20 (10)	0.40	0.55 (0.15–1.77)
LYQC	4 (5.7)	5 (2.5)	0.36	2.36 (0.51–10.52)
LYPA	1 (1.4)	4 (2)	0.83	0.71 (0.03–6.90)

* Yates corrected

Clinical comparison of MBL polymorphisms

Clinical data of the patients in association with MBL polymorphisms were analyzed. Mean onset age of symptoms in those patients with heterozygous (A/O) or homozygous (O/O) genotypes for any of the exon 1 alleles did not differ from those patients who were homozygous for wild-type coding allele (A/A) (43.33 vs. 18.25 months, respectively; $P = 0.199$). The age at onset of the diseases was further analyzed according to the promoter haplotype, which did not show any significant differences by the presence or absence of the low-producing LXP haplotype (14.25 vs. 40.61 months, respectively; $P = 0.12$) and intermediate-producing LYA haplotype (20.67 vs. 41.10 months, respectively; $P = 0.322$).

Some clinical findings were consequently compared between the groups who were heterozygous (A/O) or homozygous (O/O) and also based on the presence or absence of the LXP and LYA haplotypes, but we did not find any significant differences among these groups. In addition, classification of the genotypes into three groups based on their association with serum MBL levels [27], did not show any significant difference in frequency of complications among these groups (Table 5).

We also analyzed MBL polymorphisms in two groups of CVID patients with and without autoimmunity. Heterozygous (A/O) genotype, which was significantly overrepresented in the patient group, was the most common genotype in both groups with autoimmunity (6 of 11 cases, 54.5%) and without autoimmunity (18 of 24 cases, 75%) ($P = 0.263$). There was also no significant difference on frequencies of the haploypes between these groups: LYPB haplotype was detected in 54.5% of the CVID patients with autoimmunity and 66.6% of the patients without autoimmunity ($P = 0.708$).

Discussion

Common variable immunodeficiency is the most common symptomatic primary immunodeficiency. In addition to some known defects of B and T cells, which could lead to decreased serum levels of IgG, IgA and IgM [32], non-antibody mediated components of the immune system might have critical role in CVID. Recently, the association of some polymorphisms in proinflammatory cytokines and CVID was reported, which could lead to higher production of TNF-α [33]. It is assumed that pathogen associated molecular pattern recognition by immune components such as MBL could also be a compensatory mechanism in CVID. It is proposed that impaired MBL-mediated immunity in CVID patients leads to recurrent infections at an earlier age [28]. There are several reports on the role of complement deficiencies in CVID patients, while the possible contribution of defects in the classical and alternative pathways has been uncertain [34, 35].

In this study, we have carried out an association study on six SNPs of the MBL gene in CVID patients and healthy individuals. The results of our study showed that the codon 54 mutation (G–A) and B allele of the MBL gene might be more frequent in CVID patients than healthy subjects. Whereas the wild-type (A) allele is less common in CVID patients than controls. Similarly, exon 1 genotype analysis showed that those subjects heterozygous for exon 1 alleles are significantly associated with CVID, compared with the control subjects. In addition, homozygous genotype for

Table 5 Comparison of mean age and some clinical characteristics among different genotypes groups based on their association with serum MBL levels

Characteristics	Genotypes groups*		
	Normal MBL production[a]	Low MBL production[b]	Deficient MBL production[c]
Number of cases	7	22	6
Onset age (months)	18.1	48.5	20.3
Diagnosis age (months)	133.5	120.7	101.0
Delay diagnosis (months)	115.4	72.2	80.6
Bronchiectasis	3 (43%)	11 (50%)	2 (33%)
Splenomegaly	3 (43%)	10 (45%)	2 (33%)
Autoimmunity	3 (43%)	7 (32%)	1 (17%)

* Classification based on the reference 30

[a] *HYA/HYA* and *HYA/LYA* genotypes were considered to be associated with normal levels of serum MBL

[b] *HYA/LYB*, *HYA/LYC*, *HYA/LYD*, *LYA/HYD*, *LYA/LYB* and *LXA/LXA* genotypes were considered to be associated with low levels of serum MBL

[c] *HYD/LYB*, *LYB/LYC*, *LXA/LYB* and *LXA/LYC* genotype were considered to be associated with deficient levels of serum MBL

wild-type exon 1 alleles is significantly less common in the CVID patients than the controls.

Mutated allele of codon 54 is the most frequent mutation for MBL gene in our population similar to that of other populations, such as European populations. Mutated alleles could confer the low-producing phenotype and impaired MBL pathway as a critical component in CVID patients. Theoretically, those patients with low-producing alleles and impairment in MBL pathway, as a compensatory component in the immune system, are more susceptible to infections leading to earlier presentation of disease. In a study by Mullighan et al. no significant association was observed between MBL polymorphisms and susceptibility to CVID, while they indicated that patients with low-producing MBL alleles manifested significantly earlier than those with high-producing MBL alleles [28]. Another study by Fevang et al. showed that increased complement activation significantly associated with signs of autoimmunity and immunologic hyperactivity. Furthermore, they found that patients with recurrent lower respiratory tract infections or bronchiectasis had lower capacity of the lectin pathway than patients without these feature; the serum level of MBL was inversely correlated to the frequency of lower respiratory tract infections and bronchiectasis [36]. In a recent study by Litzman et al. such finding was not confirmed, but they found an association between low-producing genotypes and development of bronchopulmonary complications [27]. Because the role of MBL pathway in autoimmunity and infections has been shown in different studies, we investigated the association of each allele and haplotype with certain clinical condition in patients. Among 35 CVID patients in our study, splenomegaly and autoimmunity was detected in 15 and 11 subjects, respectively. Sixteen cases had bronchiectasis due to recurrent pneumonia. However, no significant association between MBL alleles and certain clinical condition was found. Thus, in contrast to those studies, we have not found any significant difference regarding neither the mean age of onset/diagnosis nor clinical manifestations and specific MBL genotypes/haplotypes. However, it should be noted that relatively small sample size is one of the limitations of our study.

Haplotype analysis in our study showed that LYPB haplotype is significantly more common in CVID patients than controls. Some of these associations have not been previously reported.

In conclusion, it is demonstrated that mutant alleles might reflect as an associated genetic factor in CVID patients, which could play as a susceptibility factor in CVID. Future studies are needed to investigate simultaneously serum MBL level, complement level and lectin pathway activity in a large sample of patients. Once these associations are confirmed, this may lead to improved and individualized patient care for this heterogeneous population.

Conflict of interest statement The authors declare that they have no conflict of interest related to thepublication of this manuscript.

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