Association of Single-Nucleotide Polymorphisms of the MBL2 with Atopic Dermatitis in Korean Patients

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Background: Human mannose-binding lectin (MBL) is a serum lectin taking part in the innate immunity by opsonizing various microorganisms for phagocytosis. The MBL serum concentration is affected by several single-nucleotide polymorphisms (SNPs) in the promoter region of the MBL2 gene. Objective: The purpose of this study was to examine the relationship between MBL2 polymorphisms and atopic dermatitis (AD) susceptibility. Methods: To examine whether the MBL2 SNPs are related to AD susceptibility, we examined 237 patients with AD and 94 controls by polymerase chain reaction (PCR)-restriction fragment length polymorphism and PCR-sequence specific primer analyses of four polymorphic loci: two (H/L and X/Y) within the promoter region and the other two (P/Q and A/B) within exon 1. MBL concentrations in the blood were estimated by ELISA. Results: The prevalence of haplotype HYPB, leading to MBL deficiency, was significantly decreased in the AD patients compared to the controls (p=0.002), while the prevalence of haplotype HYPA was increased with a clear trend toward significance (p=0.056). The frequency of MBL2 LYPB/LXPA (odds ratio, 0.08; 95% confidence interval, 0.009 ∼ 0.655; p=0.021) were significantly decreased in the AD patients. The blood log [total immunoglobulin E, IgE] levels of MBL2 HYPA/HYPA, HYPA/LYPA, HYPA/LYPB, HYPA/LYQA, and LYQA/LXPA haplotype pairs were significantly increased in the AD patients. Conclusion: The frequency of MBL2 HYPB haplotype was significantly decreased in the AD patients compared to the controls. The frequency of LYPB/LXPA had a possibly protective effect on AD. Moreover, the MBL2 HYPA haplotype pairs, which were related to higher blood total IgE levels, were possibly associated with extrinsic AD.

Keywords- Atopic dermatitis, Innate immunity, Mannose-binding lectin

INTRODUCTION

Atopic dermatitis (AD) is a type of skin inflammation that is caused by both genetic and environmental factors. Human mannose-binding lectin (MBL) is a serum lectin taking part in the innate immunity by binding various microorganisms and activating the lectin-complement. Opsonization defect due to deficiency of MBL is associated with increased susceptibility to infection and stems from the presence of a low efficiency promoter and/or three gene mutations in exon 1 (variants B, C, and D) of MBL2. The patients with abnormal homozygous MBL alleles are susceptible to an immune-deficiency disease that is not related to HIV. MBL deficiency could trigger AD or complications when they are additionally exposed to an infection. The first evidence of MBL involvement in AD was suggested by a family study which showed that children with low plasma MBL levels who were homozygous for allele B of MBL were prone to pruritic skin disease and possibly AD, with or without recurring infections. In addition, a report revealed that low MBL levels were clearly associated with the BB MBL2 haplotype in a Turkish family members who...
also had recurrent skin infections and AD. Moreover, the three exon 1 variants B, C, and D of MBL were more frequently observed in Brazilian AD patients than in healthy controls, although the disease severity was not investigated. In this study, children with AD had higher frequency of allele O of MBL gene related to low or deficient levels of MBL compared to the control group. Likewise, low or deficient serum MBL levels may result in predisposition to AD, although there was a conflicting report that showed no association of the B allele of MBL with AD susceptibility in a Japanese population.

We hypothesized that the modulation of innate immune defense by MBL2 variants influenced a wide range of susceptibility to AD. Therefore, we investigated whether single-nucleotide polymorphisms (SNPs) of the MBL2 gene could be proper genetic diagnostic factors in Korean AD patients by examining the SNPs and haplotypes, including −550 and −221 in the promoter region, +4 in the 5′ UTR and codon 54 in exon 1 of the MBL2 gene.

MATERIALS AND METHODS

Subjects

In this study, we included 237 unrelated Korean AD patients (132 males and 105 females; mean age 32.5±18.0 years; age range 5~90 years) who were registered in the Department of Dermatology, Uijeongbu St. Mary’s Hospital in Korea. All patients showed moderate to severe AD according to the Hanifin’s criteria. Controls were 94 healthy persons without a personal or family history of AD. For genetic studies, blood was collected by venipuncture, and genomic DNA was prepared using QIAamp blood kit (Qiagen, Hilden, Germany). Blood [total immunoglobulin E, IgE] was measured by LPIA-200 system (Iatron Corp., Tokyo, Japan). Blood IgE levels were measured in a double-enzyme immunoassay with an anti-MBL mAb (clone HYB-131; State Serum Institute, Copenhagen, Denmark) according to the manufacturer’s directions. An antigen-specific IgE antibody to Dermatophagoides pteronyssinus (Dp) and Dermatophagoides farina (Df) were performed with the Pharmacia CAP FEIA immunoassay on a UniCAP 100 automatic analyzer (Pharmacia and Upjohn, Uppsala, Sweden) according to the manufacturer’s directions. An antigen-specific IgE value of over 0.35 kU/L was classified as increased. The clinical data are presented in Table 1. This study was carried out from March 3, 2003 to December 25, 2004 in compliance with the principles of the Declaration of Helsinki. Since there was no statutory law during that time, only verbal consent was obtained from the patients and healthy persons after explaining the purpose of our study and their rights. In case of children were included in the study, the parent or guardian was informed orally and they agreed to the purpose and procedure of our study. The coded research data obtained from March 3, 2003 to December 25, 2004 were reanalyzed and the Institutional Review Board (IRB) of Uijeongbu St. Mary’s Hospital approved this study on November 12, 2015 (IRB no. UC15RISI0160).

Molecular methods

Primer sets were designed for the four polymorphic sites: H/L at −550, X/Y at −221, P/Q at +4, and A/B at codon 54 (Fig. 1A), and used for differential PCR analysis. Genotyping of the promoter region at position −550 (rs-11003125) of the MBL2 gene and codon 54 (rs1800450) of exon 1 was carried out by the polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) analysis as described before. Genotyping of the promoter region at position −221 (rs7096206) of the MBL2 gene was performed by the PCR-sequence specific primer method, as described by Steffensen et al. DNAs with one point mutation in the 5′ UTR at position +4 (P/Q variants) of the MBL2 gene were amplified by site-directed mutagenesis (SDM)-PCR. The P and Q alleles were detected by RFLP performed on the SDM-PCR products using a mutated 5′-primer (Table 2). AccI cleaved the 261 bp PCR product specific for the L allele into two fragments (239 bp and 22 bp), while BanI cleaved the A and B alleles. SacI and HindIII cleaved the 136 bp PCR products specific for the P and Q alleles into 110 bp and 26 bp fragments, respectively. PCR restriction fragments were separated by 8% polyacrylamide gel electrophoresis.

Assay for blood MBL levels

Blood MBL levels were measured in a double-enzyme immunoassay with an anti-MBL mAb (clone HYB-131; State Serum Institute, Copenhagen, Denmark).

Table 1. Clinical profiles of the study subjects

| Clinical profile | Atopic dermatitis patient | Control |
|------------------|--------------------------|---------|
| No. of subjects  | 237                      | 94      |
| Age (yr)         | 32.5 (5~90)              | 43.2 (13~62) |
| Sex (male/female)| 132/105                  | 77/17   |
| Log [total IgE]±SD| 5.54±1.74*               | 4.19±1.31 |
| Positive rate of specific IgE (Dp) | 54% | - |
| Positive rate of specific IgE (Df) | 55% | - |

Values are presented as number only, mean (range), log [total IgE]±SD, or percent only. IgE: immunoglobulin E, SD: standard deviation, Dp: Dermatophagoides pteronyssinus, Df: Dermatophagoides farina. *p-value<0.0001 for the difference between atopic dermatitis patients and normal controls.
A Map of the MBL gene located on chromosome 10q11.2-q21

\[ D = 0.03, D' = 1 \]
\[ D = 0.02, D' = 0.4 \]
\[ D = 0.05, D' = 0.4 \]
\[ D = 0.01, D' = 0.6 \]

GRE box
GC box
HSE
-550
TATA box
-221
CCAAT box
Collagen-like domain

B MBL haplotypes

| Haplotype | MBL-550 G>C | MBL-221 G>C | MBL+4 C>T | MBL+230 G>A | Frequency |
|-----------|-------------|-------------|-----------|-------------|-----------|
| ht1 (HYPA) | G           | G           | C         | G           | 0.458     |
| ht2 (LYPA) | C           | G           | C         | G           | 0.187     |
| ht3 (LYPB) | C           | G           | C         | A           | 0.159     |
| ht4 (LYQA) | C           | G           | T         | G           | 0.070     |
| ht5 (LXPA) | C           | C           | C         | G           | 0.054     |
| ht6 (HPYPB) | G          | G           | C         | A           | 0.038     |
| ht7 (HYQA) | G           | G           | T         | G           | 0.021     |
| Others     |             |             |           |             | 0.014     |

C LD coefficients \(|D'| (p-value)\) among MBL SNPs

\[ D/D' r^2 \]

| SNP | MBL-550 G>C | MBL-221 G>C | MBL+4 C>T | MBL+230 G>A |
|-----|-------------|-------------|-----------|-------------|
| G>C | 0.998 (<0.0001) | 0.413 (0.003) | 0.439 (<0.0001) |
| D=0.034 | 0.021 | 0.046 |
| \(r^2=0.073\) | 0.020 | 0.052 |
| -221 G>C | 0.091 (0.063) | 0.231 (0.427) |
| 0.005 | -0.003 |
| 0.005 | 0 |
| +4 C>T | 0.599 (0.01) | -0.012 |
| 0.010 |
| +230 G>A | - |

Statistics

Hardy-Weinberg equilibrium was analyzed for the gene frequencies obtained by simple gene counting and the chi-square test was performed for comparing the observed and expected values. We examined a widely used measure of linkage disequilibrium (LD) between all pairs of bi-allelic loci, Lewontin’s \(D' (|D'|)\)\(^\text{15}\). Haplotype frequencies were calculated using the Phase 2.0 program, as described elsewhere\(^\text{16}\). Phase probabilities of each site were also calculated for each individual by the Phase 2.0 program. Individuals with phase probabilities less than 0.987 were excluded from the analysis. Genetic effects of inferred haplotypes were analyzed in the same way as SNPs. Comparison of genotype and haplotype frequencies for each MBL2 polymorphism was carried out by chi-square test. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using SAS ver. 8.1 (SAS Institute, Cary, NC, USA). \(p<0.05\) after Bonferroni’s adjustment for multiple testing of the four SNPs in the diploidy was considered to be statistically significant throughout the study. An OR provides an effect estimate, whereas a score of < 1 is related to a protective effect, and a score of > 1 is related to an increased risk. Genotype distribution of MBL2 SNPs and haplotypes among AD patients and normal controls were analyzed with logistic regression models adjusted for age, sex and log [total blood IgE] levels as covariates.
| Locus       | Group | Genotype | Frequency* | HW † | p-value ‡ |
|------------|-------|----------|-----------|------|----------|
| MBL−550 G>C | AD    | GG       | 68 (28.7) | 58 (24.5) | 0.479 | 0.23 | 0.92 |
|            | NC    | GG       | 26 (27.7) | 25 (26.6) | 0.495 |       |
| −221 G>C   | AD    | GG       | 210 (88.6) | 26 (11) | 1 (0.4) | 0.060 | 1 | 0.38 |
|            | NC    | GG       | 79 (84.0) | 15 (16.0) | 0 (0) | 0.080 |       |
| +4 C>T     | AD    | CC       | 194 (81.9) | 41 (17.3) | 2 (0.8) | 0.095 | 1 | 0.81 |
|            | NC    | CC       | 74 (78.7) | 19 (20.2) | 1 (1.1) | 0.112 |       |
| +230 G>A   | AD    | AG       | 150 (63.3) | 77 (32.5) | 10 (4.2) | 0.205 | 0.50 | 0.54 |
|            | NC    | AG       | 62 (66) | 26 (27.7) | 6 (6.4) | 0.202 |       |

Values are presented as number (%). *Minor allele frequencies. † p-values of deviation from Hardy-Weinberg (HW) equilibrium in total subjects (n=331). ‡ p-values for chi-square test.

RESULTS

Characteristics of the study population

The clinical characteristics of 331 subjects are shown in Table 1. Mean age was higher in the controls compared to the patients, and males were predominated in both groups. Around 54% of the patients with AD were positive for Dp-specific IgE and 55% of patients were positive for Df-specific IgE. Subjects with AD had higher blood log [total IgE] levels (Student’s t-test, p < 0.0001).

Allele frequencies of the MBL polymorphisms

The MBL2 gene located on chromosome 10q11.2-q21 consists of four exons with a total size of ~10.0 kb. Four SNPs in the MBL2 gene (Fig. 1A); three within the upstream of the promoter region (a G-C transversion at position 550, a C-G transversion at position 221, and a C-T transition at position +4 in the 5’ UTR) and one G-A transition at +230 calculated on the codon 54 of exon 1 were genotyped by the single-base extension method. As shown in Fig. 1, MBL −550 G>C, −221 G>C, +4 C>T and +230 G>A were included in the statistical analysis. All four SNPs were in complete (|D'| = 1 and r² ≠ 1) or absolute LD (|D'| = 1 and r² = 1). Seven haplotypes were identified without any ambiguous phasing due to LDs among SNPs (Fig. 1B, C).

Allele distributions of the polymorphisms on MBL2 (MBL −550 G>C, −221 G>C, +4 C>T, and +230 G>A)
Table 4. Comparison of haplotype frequencies of the MBL gene between patients with AD and controls

| MBL haplotype | AD 2N-474 (n=237) | Control 2N-188 (n=94) | p-value |
|---------------|-------------------|------------------------|---------|
| HYPA          | 0.481 (228)       | 0.399 (75)             | 0.056   |
| LYPB          | 0.173 (82)        | 0.223 (42)             | 0.134   |
| LYPB/LYPB     | 0.049 (23)        | 0.069 (13)             | 0.065   |
| LYPB/LYQA     | 0.070 (33)        | 0.069 (13)             | 0.983   |
| HYPA/LYPB     | 0.023 (11)        | 0.075 (14)             | 0.002   |
| HYPA/LYQA     | 0.017 (8)         | 0.032 (6)              | 0.225   |
| Others        | 0.013 (6)         | 0.013 (3)              | 0.741   |

( ): number of cases. AD: atopic dermatitis. p-values were calculated by chi-square test.

Table 5. Comparison of frequencies of MBL haplotype pairs between patients with AD and controls

| MBL haplotype pair | AD (n=237) | Control (n=94) | p-value | OR (95% CI) |
|--------------------|------------|----------------|---------|-------------|
| HYPA/HYPA          | 51 (21.5)  | 9 (9.6)        | 0.077   | >0.999      |
| LYPB/LYPB          | 9 (3.8)    | 5 (5.3)        | >0.999  | >0.999      |
| LYPB/LYPB/LYPB     | 4 (1.7)    | 0              | >0.999  | >0.999      |
| LYPB/LYQA/LYPB     | 6 (2.5)    | 1 (1.1)        | >0.999  | >0.999      |
| LYPB/LXPA/LYPB     | 1 (0.4)    | 5 (5.3)        | 0.021   | 0.08 (0.009 ∼ 0.655) |
| HYPA/HYPA/LYPB     | 2 (0.8)    | 1 (1.1)        | >0.999  | >0.999      |
| HYPA/LYPA/LYPB     | 1 (0.4)    | 0              | >0.999  | >0.999      |

Values are presented as number (%). AD: atopic dermatitis. OR: odds ratio, 95% CI: 95% confidence interval. p-values were calculated by chi-square test after Bonferroni’s adjustment for multiple testing.
Table 6. Comparison of plasma MBL levels in MBL haplotype pairs between patients with AD and controls

| MBL haplotype pair | AD (mg/L, n=237) | Control (mg/L, n=94) | p-value |
|--------------------|------------------|----------------------|---------|
| HYPA/HYPA          | 5,154.7±2,106.1 (54) | 4,500.2±1,439.2 (14) | 0.277   |
| HYPA/LYPA          | 4,519.2±1,933.6 (41) | 3,862.0±1,434.5 (23) | 0.160   |
| HYPA/LYPB          | 1,413.7±1,561.3 (51) | 1,159.1±1,414.3 (9)  | 0.650   |
| HYPA/LYQA          | 4,084.4±1,384.2 (16) | 4,847.3±1,512.3 (9)  | 0.213   |
| HYPA/HYPB          | 444.6±2,166.0 (6)   | 3,031.7±2,619.7 (3)  | 0.414   |
| HYPA/HYQA          | 5,489.9±1,245.8 (6) | 5,172.2±1,689.4 (3)  | 0.756   |
| LYPB/LYPA          | 2,189±1,688.4 (6)   | 3,128.2±2,000.4 (4)  | 0.445   |
| LYPB/LYPB          | 1,234.5±1,557.8 (9) | 1,051.5±1,049.1 (5)  | 0.820   |
| LYPB/LXPA          | 2,885.5±1,608.4 (16)| 2,961.1±2,450.6 (5)  | 0.858   |
| LYPB/LYPB          | 1,037±975.5 (6)     | 869.5±UD (1)         | 0.880   |
| LYPB/LYQA          | 878.3±UD (1)        | 761.1±1,240.3 (5)    | 0.936   |
| LYPB/Other          | 289.1±512.5 (5)     | 673.6±UD (1)         | 0.531   |
| LYQA/LXPA          | 2,912.3±1,710.8 (4) | 2,749.8±440.6 (2)    | 0.906   |
| HYPB/LYPB          | 444.6±2,166.0 (6)   | 3,031.7±2,619.7 (3)  | 0.414   |
| HYPB/HYQA          | 5,489.9±1,245.8 (6) | 5,172.2±1,689.4 (3)  | 0.756   |

Values are presented as mean±standard deviation (number of cases). AD: atopic dermatitis, UD: undetectable. P-value was calculated by t-test.

Table 7. Comparison of log [total immunoglobulin E] levels in MBL haplotype pairs between patients with AD and controls

| MBL haplotype pair | AD (n=237) | Control (n=94) | p-value |
|--------------------|------------|---------------|---------|
| HYPA/HYPA          | 5.36±1.94 (54) | 4.32±1.15 (14) | 0.014   |
| HYPA/LYPA          | 5.49±1.79 (41) | 4.16±1.45 (23) | 0.004   |
| HYPA/LYPB          | 5.82±1.80 (51) | 4.08±1.01 (9)  | 0.007   |
| HYPA/LYQA          | 5.74±1.54 (16) | 4.21±1.02 (9)  | 0.014   |
| HYPA/HYPB          | 5.59±2.00 (6)  | 2.56±1.76 (3)  | 0.064   |
| HYPA/HYQA          | 6.34±1.31 (6)  | 4.57±0.62 (3)  | 0.061   |
| LYPB/LYPA          | 5.19±1.68 (6)  | 4.41±1.44 (4)  | 0.468   |
| LYPB/LYPB          | 5.33±1.49 (9)  | 4.36±0.93 (5)  | 0.217   |
| LYPB/LXPA          | 5.11±1.49 (16) | 3.80±1.53 (6)  | 0.083   |
| LYPB/LYQA          | 5.95±1.65 (6)  | 4.63±UD (1)    | 0.491   |
| LYPB/LYPB          | 3.31±UD (1)    | 4.94±2.18 (5)  | 0.531   |
| LYPB/Other          | 5.04±1.46 (5)  | 1.63±UD (1)    | 0.10    |
| LYQA/LXPA          | 7.27±1.31 (4)  | 4.04±1.13 (2)  | 0.042   |
| HYPB/LYPB          | 6.74±1.48 (2)  | 4.42±UD (1)    | 0.423   |
| HYPB/HYPB          | 4.76±UD (1)    | 4.15±1.27 (4)  | 0.698   |
| HYPB/HYQA          | 4.90±UD (1)    | 3.90±1.18 (2)  | 0.614   |

Values are presented as mean±standard deviation (number of cases). AD: atopic dermatitis, UD: undetectable. P-value was calculated by t-test.

HYPA haplotype, the most effective MBL-producing haplotype, was found in Asians including Koreans (0.44 ∼ 0.47) and Caucasians (0.25 ∼ 0.34) and commonly in Eskimos (0.81). In contrast, the LXPA haplotype was found rarely in Asians including Koreans (0.07 ∼ 0.10) and Eskimos (0.03), but it was found more commonly in Caucasians (0.18 ∼ 0.26)23,31,12,18.

Various genetic polymorphisms in the MBL gene have been reported as risk factors for the development of a certain clinical subtype and severity. The susceptibility to Behcet’s disease (BD) is related to a higher frequency of the MBL2 HYPA haplotype, which may cause increased acute or chronic hyper-inflammatory responses and influence the severity of BD35. A significantly higher percentage of patients with BD showed high serum MBL levels (≥ 500 ng/ml) compared to controls and were associated with skin lesions in Korean patients20. In addition, the progression of systemic lupus erythematosus is associated with MBL gene polymorphism and serum MBL concentration21.

In our study, the blood MBL levels were significantly correlated with total IgE levels in the AD patients. In addition, blood log [total IgE] levels of MBL2 HYPA/HYPA, HYPA/LYPA, HYPA/LYPB, HYPA/LYQA, and LYQA/LXPA haplotype pairs were significantly increased in the AD patients. Extrinsic AD shows high total plasma IgE levels and has specific IgE for environmental and food allergens, whereas intrinsic AD shows normal total IgE levels and the absence of specific IgE22. Our previous study demonstrated that the polymorphisms of the macrophage migration inhibitory factor (MIF) promoter related to innate immunity were significantly associated with an increased risk for AD. Especially, the −794 7-CATT locus and the MIF C/7-CATT haplotype were significantly associated with decrease of total IgE levels in the blood, suggesting that these polymorphisms might be a marker for intrinsic AD23. Therefore, the HYPA haplotype pair of the MBL2 gene, which is related to higher total blood IgE levels, would be a possible marker for extrinsic AD.

In conclusion, we investigated the SNPs and the hap-
lotypes of the MBL2 gene, which might be proper genetic diagnostic factors in Korean AD patients. The frequency of MBL2 LYPB/LXPA had a possibly protective effect in Korean AD patients.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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