Are mannose-binding lectin gene 2 (MBL2) polymorphisms and MBL deficiency associated with infections?

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Mannose-binding lectin (MBL) is an important element of the innate immune system. MBL binding leads to activation and cleavage of C3 and C4, suggesting the role of the MBL pathway for opsonization and phagocytosis. The role of adaptive immune response in the development of pathogenic autoantibodies in various autoimmune diseases is well understood. The link between innate and acquired immunity is helpful for understanding the immunopathogenesis of autoimmune diseases. Evidence that the innate immune system could lead to autoimmunity is growing with the major recent concept that autoimmune disease pathogenesis is related to impaired apoptotic cell clearance. MBL has been demonstrated to facilitate clearance of apoptotic cells in vivo and in vitro. Low MBL serum levels resulting in impaired apoptotic clearance have shown to enhance the risk for infection and high MBL serum levels and high MBL activity have been associated with inflammatory autoimmune diseases like systemic lupus erythematosus (SLE), which, in turn, results in tissue damage and, finally, leads to organ damage. Serum MBL levels fluctuate during the course of SLE disease activity, and MBL genotypes have been found to be useful in assessing the risk of infection during the immunosuppressive treatment that the majority of the SLE patients receive.[1]

In this issue, Demirhan et al. presented the first report that describes the association of MBL-2 polymorphisms with infection in children with Down syndrome (DS) from Turkey. This study gives a distribution of MBL-2 exon 1 genotypes (Codon 54 and 57) in a large number of DS patients and normal healthy individuals. Demirhan et al.’s study provides an evidence that a homozygote or heterozygote for a different MBL-2 allele is not associated with infections in patients with DS and do not influence the incidence of infections.[2] The gene encoding MBL, MBL2 (MBL1 is a pseudogene), is located on chromosome 10q11.2-q21 and contains four exons. A number of single-nucleotide polymorphisms (SNPs) have been characterized in the gene. Exon 1 harbors three missense SNPs giving rise to amino acid exchanges in the first part of the collagenous region. Two of these (Gly54Asp, named “B” and Gly57Glu, “C”) exchange glycine with an acetic amino acid. The third (Arg52Cys, “D”) introduces a cysteine in the collagen region (the residue numbers includes the leader sequence of 20 residues). The wild type is denoted “A.” The three variant structural alleles are associated with decreased MBL levels. The promoter region shows a number of SNPs as well, some of which influence the expression of MBL, like the polymorphisms at –550 (termed H/L), –221 (termed Y/X) and –66 (termed P/Q). Because of linkage disequilibrium, only seven haplotypes are found; HYPA, LYP, LYQA, LXPA, HYPD, LYPB and LYQC, giving a total of 28 possible genotypes (e.g., the MBL-deficient genotype: LXPA/LYPB). Individuals homozygous for A show MBL levels above 1 ng/ml, except some of those homozygous for LXPA. Heterozygous people with A on
one gene and B, C or D on the other mostly have MBL
levels between 0.5 and 1 ng/ml, while those with variant
structural allotypes on both genes (genotypes often
denoted 0/0) show MBL levels below 50 ng/ml. Such
low levels are also found in individuals with LXPA on
one gene and B, C or D on the other. The frequency of
the haplotypes differs between ethnic groups, with, e.g.,
LYPB being the common variant haplotype in Caucasians
(12%) and Asians (22%), but very rare in Africans. In
contrast, LYQC is the common variant haplotype in
Africans (24%) but is rarely found in Caucasian and Asian
people. It is not always realized that the LXPA haplotype,
with a gene frequency of 24%, is the most common cause
of MBL deficiency in Caucasians, either presented as
homozygous LXPA individuals (where the concentration
is somewhat unpredictable) or in concert with a variant
haplotype, always resulting in very low levels.[3]

Most subjects who are MBL-deficient appear to remain
healthy. However, low serum MBL levels and their
cognate haplotypes have been associated with a range
of bacterial infections in both children and adults. The
wide variety of pathogens involved in these infections is
typical of an immunodeficiency. However, the fact that
most MBL-deficient people do not get infections had led
to speculation that a second immune defect needs to be
present for susceptibility to infection, leading to several
primary and secondary immunodeficiency syndromes.[4-8]

**Immunodeficiency and Low Mannose-Binding Lectin
Levels**

Common variable immunodeficiency (CVID) is a
heterogeneous syndrome characterized by failure of
B cell differentiation and defective immunoglobulin (Ig)
production, leading to recurrent bacterial infections,
particularly in the respiratory tract. Although reduced
Ig secretion from B cells is the hallmark of CVID, other
immunological abnormalities such as T cell dysfunction
and monocyte/macrophage hyperactivity are seen in a
considerable proportion of patients. These abnormalities
may be important for both the B cell deficiency as well as
for some of the clinical manifestations in these patients,
such as increased frequency of autoimmune disorders,
granulomatous inflammation and malignant and
nonmalignant lymphoid hyperplasia.[2,8,9] In syndromes as
diverse as CVID, human immunodeficiency virus/acquired
immunodeficiency syndrome and chemotherapy-induced
neutropenia, the presence of variant MBL alleles is
associated with earlier, more frequent and more
severe infection. Presumably, the co-existence of MBL
deficiency increases infection susceptibility, allowing
further rapidly progressive lung and liver disease. Thus,
MBL deficiency may affect susceptibility to a disease
(e.g., meningococcal disease) or alter the natural history
of a disease, such as cystic fibrosis, CVID and chronic
granulomatous disease.[5,10,11]

DS is associated with a significant health burden,
which is particularly apparent in young children who
will frequently present with cardiac and respiratory
problems. Children with DS have a high prevalence of
respiratory infections. Such infections are more often
seen in children who have congenital heart disease and
pulmonary artery hypertension. Otitis media also has
been noted more often in children with DS. Demirhan
et al. have provided valuable information about the low
expression of heterozygosity, which is not a major risk
factor for infections in this study, suggesting that it may
be associated with protection against infections. As there
are some conflicting evidences of MBL deficiency and
associated infections,[12,13] we feel that additional data
on the types of infections in DS patients, MBL promoter
region polymorphisms, namely -550 H/L (G→C), -221
Y/X (G→C), +4 P/Q (C→T), and serum MBL levels should
support these findings. Such data should be evaluated by
statistical analysis. Still, we feel that Demirhan et al. have
made a beginning in this area as this is an indexed study
that gives an insight for further studies in DS patients
from other parts of the world to understand the associated risk
of MBL deficiency and MBL genotypes with infections.
Such studies may further throw some light on the possible
correlation between high-expression MBL-2 genotypes
and the associated biological functions of MBL.

**References**

1. Pradhan V, Surve P, Ghosh K. Mannose binding lectin
gene polymorphism in Systemic Lupus Erythematosus
2. Demirhan O, Tastemir D, Gunesacar R, Guzel AI,
Alptekinv D. The first report described as an important


