Review Article: Is there a relationship between Systemic Lupus Erythematosus and the Mannose Binding Lectin gene?

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Abstract:
Our review article discusses the relationship between systemic lupus erythematosus and the mannose-binding lectin gene. The complex trait of systemic lupus erythematosus (SLE), which manifests as a variety of clinical phenotypes and the production of several autoantibodies, is SLE. SLE patients experience a wide range of clinical phenotypes, such as skin rash, and neuropsychiatric, and musculoskeletal symptoms, some of which can progress to lupus nephritis. Abnormal complement activation causes inflammation, which damages multiple organs' tissue. About 50% of systemic lupus erythematosus patients, a chronic inflammatory disease, experience kidney damage. Despite effective anti-inflammatory and immunosuppressive therapies, lupus nephritis still results in end-stage kidney impairment (ESRD) or chronic kidney disorder (CKD) for an excessive number of patients. It represents a significant risk factor regarding mortality and morbidity in SLE. The family of C-type lectins of collectins includes the mannose-binding lectin (MBL), whose portion in the pre-immune first line of defense seems to involve pattern recognition. MBL can identify carbohydrate modes that abound on the surfaces of numerous pathogenic bacterial, viral, protozoal, and fungal microorganisms. The complement system's lectin pathway is activated when MBL binds to a microorganism. Numerous studies have linked MBL polymorphism, SLE, and lupus nephritis.

Keywords: Systemic lupus erythematosus (SLE), Lupus nephritis, Mannose-binding lectin (MBL).

Introduction
A chronic inflammatory condition called systemic lupus erythematosus (SLE) is defined by an autoantibody response to cytoplasmic and nuclear antigens. It progresses in an occurring, relapsing situation fashion. Greater than ninety percent of SLE patients involve women, and they typically begin while they are of childbearing age.¹ The development is thought to be influenced by both environmental and hereditary influences.² These environmental and hereditary influences lead to immune system flaws.³ SLE risk factors include exposure to the
sun, smoking, deficiency of vitamin D, and particular infections in addition to female sex hormones.\(^{(2)}\)

**Epidemiology**

In the US, there are 20–150 cases of Systemic Lupus Erythematous (SLE) per 100,000 people.\(^{(4-7)}\) Rates of prevalence per 100,000 women vary from 164 in white people to 406 in African Americans.\(^{(4)}\) At the end of the twenty-eth century, regarding 40 years occurrences nearly tripled as a result of better identification of mild diseases.\(^{(8)}\) About 1 and 25 cases per 100,000 people occur in the Americas, Latin America, Europe, and Asia.\(^{(5, 9-11)}\)

The prevalence of SLE, as well as the pattern and seriousness of medical conditions and diagnostic studies, are influenced by geographic presentation and race:

- The disease is more widely spread in cities than in rural areas.\(^{(4, 12)}\) Compared to White people, SLE is more common in Asian, African, American, Caribbean, and Hispanic American populations.\(^{(5, 9-10, 12)}\) SLE is a rare occurrence in Africa.\(^{(5, 13)}\)
- Patients with Northern European ancestry experience photosensitivity and discoid skin lesions more frequently than patients Many with Southern European ancestry are less likely to have antcardiolipin and anti-double-stranded DNA (anti-dsDNA) antibodies than those with Northern European ancestry.\(^{(14)}\)

**Pathogenesis**

Apoptosis seems to be important for maintaining during both homeostasis, growth, and aging. cells in apoptosis are normally consumed by using phagocytes, lysosomes and eliminated in this manner; no inflammation is involved.\(^{(15)}\) When NETosis occurs, neutrophil extracellular traps (NETs) are distributed as a controlled form of neutrophil cell death, aiding the host's defense against infections.\(^{(16)}\) According to numerous studies, SLE is caused by a faulty removal of NETs and apoptotic remains from the tissues and blood.\(^{(17, 18, 19, 20)}\) Consequently, it is commonly believed that SLE begins to show symptoms when the elimination of dead cells is compromised. There must be sufficient molecules that promote the removal of damaged cells by phagocytes from dying cells, which requires several ligands and receptors.\(^{(21)}\) Understanding this intricate mechanism offers therapeutic potential, particularly for the early detection and treatment of SLE.\(^{(22)}\) Upon losing an unbroken cell membrane, dying cells that are not removed go through secondary necrosis rapidly and effectively, and then erupt, releasing nuclear material.\(^{(23)}\) The failure of phagocytes to recognize apoptotic cells in SLE is caused by one of three factors: either the phagocytes are smaller,\(^{(24)}\) have weakened and delayed phagocytic activity,\(^{(25)}\) or differentiate less readily from CD34-positive hematopoietic stem cells.\(^{(20, 26, 27)}\)

**Laboratory tests**

The two mainstays of serologic testing for SLE are anti-extractable nuclear antigen (anti-ENA) and antinuclear antibody (ANA) testing. There are numerous methods for finding ANAs. The technique that is most frequently utilized in medicine is indirect immunofluorescence (IF). The kind of antibody serum of the subjects is shown by the fluorescence pattern. Immunoglobulin and complement protein deposits in human skin can be found via direct immunofluorescence. A positive direct IF test (also known as the "lupus band test") on skin that has
not been exposed to the sun is indicative of systemic lupus erythema-atosus. Antinuclear antibody testing is positive for many autoimmune diseases and connective tissue disorders, and it can also happen in healthy people. Anti-Smith, anti-dsDNA (related to SLE), antihistone, and antibodies against double-stranded DNA (dsDNA) are examples of subtypes of antibodies to nucleic acids (which are linked to drug-induced lupus). In people without SLE, only 0.5% have anti-dsDNA antibodies, even though they are present in 70% of instances of SLE. Anti-U1- Rib nucleoprotein (Anti-U1-RNP), which also manifests in systemic sclerosis and mixed connective tissue disease, SS-A and SS-B (all of which are more prevalent in Sjögren’s syndrome), and newborn lupus-specific risk for cardiac conduction block are other ANA that may be present in patients with SLE. Other common tests for SLE include liver enzymes, complete blood count, electrolytes and renal function (disturbed if the kidney is affected), complement system levels (low levels signal immune system consumption), and electrolytes.

**Diagnostic criteria**
The systemic lupus erythematosus (SLE) cell test, once widely utilized for diagnosis, is no longer employed because only 50–75% of SLE cases exhibit LE cells, and other instances of rheumatoid arthritis, scleroderma, and drug sensitivity also exhibit LE cells. As a result, the LE cell test is currently only occasionally conducted and only has historical importance. The right combination of clinical symptoms and laboratory data must support the diagnosis of SLE. Clinical professionals can identify SLE and subclassify this complicated disease depending focused on the target organ's symptoms with the support of familiarity with the diagnostic criteria.

The criteria established in 1982 were listed by the American College of Rheumatology (ACR). This list’s most recent revision was made in 1997. The presence of 4 out of the 11 criteria results in a sensitivity of 85% and a specificity of 95% for SLE (Table 1).

The Systemic Lupus International Collaborating Clinics (SLICC) group modified and confirmed the ACR SLE classification criteria in 2012. According to the revision, an individual is diagnosed with SLE if they have biopsy-proven lupus nephritis and ANA or anti-dsDNA antibodies, as well as 4 of the criteria, into at least 1 clinical and 1 immunologic standard (Table 2).
Table (1) lists the Systemic lupus erythematosus classification criteria that were updated in 1997 from the 1982 edition published by the American College of Rheumatology. (34)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Malar rash</td>
<td>The nasolabial folds and the malar eminences are spared by fixed erythema, whether it is flat or raised.</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>An atrophic scarring, erythematous raised patches with adherent keratotic scale, and follicular plugging may appear in older legions.</td>
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<tr>
<td>Photosensitivity</td>
<td>Skin rash brought on by unusual sun exposure, according to the patient's medical history or a doctor's observation.</td>
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<tr>
<td>Oral ulcers</td>
<td>A doctor may diagnose oral or nasopharyngeal ulceration, which is typically painless.</td>
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<tr>
<td>Arthritis</td>
<td>Non-erosive arthritis is characterized by tenderness, swelling, or effusion in two or more peripheral joints.</td>
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<tr>
<td>Serositis</td>
<td>Pleuritis symptoms include pleuritic pain or rub, or pleural effusion. Pericarditis can be seen through an ECG, rub, or pericardial effusion.</td>
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<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria greater than 0.5 grams per day OR cellular casts (RBC, granular, mixed).</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures not caused by drug use or other factors; OR psychosis not caused by drug use.</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Hemolytic anemia with reticulocytosis, leukopenia 4000/mm, lymphopenia 1500/mm, or thrombocytopenia 100,000/mm are all potential diagnoses.</td>
</tr>
<tr>
<td>Immunologic Disorder</td>
<td>Results of tests that are positive for antiphospholipid, anti-Sm, or anti-DNA antibodies.</td>
</tr>
<tr>
<td>Positive ANA</td>
<td>Enzyme-linked immunosorbent assay or immunofluorescence.</td>
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Table (2) lists the standards of the Systemic Lupus International Collaborating Clinics (SLICC). (35)

<table>
<thead>
<tr>
<th>clinical guidelines</th>
<th>Immunologic guidelines</th>
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<tr>
<td>1. Primarily, acute cutaneous lupus</td>
<td>1. ANA antibody</td>
</tr>
<tr>
<td>2. long-lasting cutaneous lupus</td>
<td>2. anti-ds DNA antibody</td>
</tr>
<tr>
<td>4. Alopecia without scarring</td>
<td>4. Antiphospholipid antibody</td>
</tr>
<tr>
<td>5. Neurologic impairment</td>
<td>5. Low complement levels</td>
</tr>
<tr>
<td>7. kidney affection</td>
<td></td>
</tr>
<tr>
<td>8. Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>9. leucopenia</td>
<td></td>
</tr>
<tr>
<td>10. Decrease in platelets number (&lt; 100,000/ mm3)</td>
<td></td>
</tr>
<tr>
<td>11. Arthritis</td>
<td></td>
</tr>
</tbody>
</table>
Mannose-binding lectin gene affection:
Our review article discusses the relationship between systemic lupus erythematosus and the mannose binding lectin gene. The serum protein known as mannose- binding lectin (MBL), also referred to as Mannose-binding protein (MBP) originated in the hepatic system. It’s a lectin that works through the lectin pathway like an immunomodulator in innate immunity. (36,37) MBL is made up of polypeptide chains with three 30-base pair peptide chains that are almost clearly identical and has an oligomeric structure (400–700 kDa). Even though MBL can take on a variety of isoforms that lack biological activity like opsonins and that minimum a tetramer form is required for complement stimulation. (38)

Polymorphisms and genes
The MBL2 gene for humans is found on chromosome 10q11.2-q21. (39) The MBL2 gene, which is located on chromosome 10, controls the production of MBL, and polymorphisms in the gene's structural regions or its promoter have been linked to relative or absolute serum MBL deficiencies. (40) The MBL2 gene has three known mutations in exon 1: codon 52 (rs5030737; C>T; Arg>Cys), known as the D variant; codon 54 (rs1800450; G>A; Gly>Asp), known as the B variant; and codon 57 (rs1800451; G>A; Gly>Glu), known as the C variant. The wild-type is A, and the variants B, C, and D are collectively referred to as O. Wild-type genotype (A/A) individuals typically have high MBL levels, whereas heterozygotes (A/O) have 10% or less of the wild-type MBL serum concentrations and homozygotes (O/O) have very low or nonexistent MBL levels. (41)

The connection between systemic lupus erythematosus (SLE) and MBL gene polymorphism:
Numerous studies have examined the relationship between MBL expression and/or concentrations in body fluids and clinical presentation as a result of mounting evidence in recent years that the MBL is essential for the innate immune response. Blood MBL levels rise in response to infections, just like the proteins of the acute phase of inflammation. The sugar moieties on the surface of bacteria, viruses, fungi, and parasites are recognized by MBL and bound to them. Through MBL-associated proteases, MBL binding causes these microorganisms to agglutinate and enables phagocytic clearance of pathogens as well as activation of the lectin-complement pathway. (42)
While non-genetic factors are also important, genetic factors account for a sizable portion of the concentration of functional MBL. (43) The functional MBL2 gene for humans is highly polymorphic. (44) In addition to promoter polymorphism, the collagenous region of MBL is altered by three independent single point mutations (SNPs) at codons 52 (Arg/Cys, allele D), 54 (Gly/Asp, allele B), and 57 (Gly/Glu, allele C). (45) The protein's collagenous structure is broken down, which lowers the percentage of higher-order oligomers in circulation and sharply lowers serum MBL concentrations. Increased MBL causes enhanced complement activation and tissue damage, while its absence has been linked to the ineffective removal of apoptotic cells, which acts as a catalyst for the production of autoantibodies. (46) Additionally, MBL deficiency is associated with a higher risk of developing secondary
infections, which is thought to play a role in the development of SLE. (47)

References

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