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## DNASE1 mutation in SLE

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## Keywords

Autoantibodies, *DNASE1*, ds DNA, mutation, nucleosome, SLE

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## Context

The gene encoding DNASE1 is about 3.2 Kb with nine exons and eight introns. It is localized to chromosome 16p13.3. Systemic lupus erythematosus (SLE) is a multifactorial disease characterized by the presence of antinuclear antibodies (ANAs) directed against naked DNA and entire nucleosomes. Mice deficient in *DNASE1* (knockout) were found to present with SLE-like symptoms, ANA-positive, deposition of immunocomplexes in the glomeruli and glomerulonephritis.

## Significant findings

Sequencing *DNASE1* of 20 Japanese SLE patients revealed two with an A ? G transversion at position +172 (exon 2), creating a premature stop codon at residue 5. The two patients were female and aged 13 years old and 17 years old with high anti-DNA and Sjorgen syndrome-A (SS-A) antibody titers. Both were heterozygous for the mutation and had substantially lower levels of DNASE1 activity than other SLE patients without the mutation and healthy controls. In addition, SLE patients without the *DNASE1* mutation had lower enzyme activity than the healthy controls. The two patients with the *DNASE1* mutation exhibited levels of nucleosomal antibodies seven to eight times higher than other SLE patients and 70-80 times greater than the healthy controls.

## Comments

These results suggest that lower levels of DNASE1 contribute to the SLE pathophysiology. The mutation was uncommon in SLE patients. It was interesting that other family members, who shared the

mutation, did not exhibit symptoms or signs of SLE. Reduced DNASE1 activity affects the rate of removal of chromatin and chromatin-protein complexes, which may influence the expansion of lymphocytes responsive to nuclear antigens. SLE patients who lack the described mutation appear to have lower levels of DNASE1 activity, suggesting that other polymorphisms may exist in the *DNASE1* regulating elements. The gene *DNASE1* does not map to an area known to be in linkage with SLE. This suggests that *DNASE1* is a disease-modifying gene or a severity marker.

## Methods

Gene sequencing, [PCR-RFLP](#), DNASE1 activity

## Additional information

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## References

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