

## **The Minor Protective Allele at rs1876453 is Associated with Increased Age of Onset of Systemic Lupus Erythematosus**

**Background:** Systemic lupus erythematosus (SLE) is a clinically heterogeneous autoimmune disease characterized by autoantibody- and complement-mediated inflammatory damage to multiple organ systems. We previously showed that the single-nucleotide polymorphism (SNP) rs1876453, located in the first intron of complement receptor 2 (CR2/CD21), is associated with decreased risk of lupus, with a preferential effect on anti-double stranded (ds) DNA antibodies. Since anti-dsDNA antibodies develop prior to clinically apparent disease, we hypothesized that the minor A allele at rs1876453 would delay lupus onset.

**Methods:** DNA from individuals recruited from multiple sites was processed with institutional review board approval. All patients with SLE met the 1997 American College of Rheumatology revised classification criteria. Age of onset was collected by chart review. Genotyping was performed on the OMRF Illumina iSelect platform. Global ancestry was estimated based on the genotype of ancestry informative markers (AIMs), using principal components analysis and ADMIXMAP, and genetic outliers removed. Final clean data were from European Americans (EA), African Americans (AA; 7.5% Gullahs), Asians (AS; 74.6% Koreans, 16.1% Chinese, 9.3% Japanese and Singaporeans) and Hispanics (HS) enriched for Amerindian–European admixture. Kruskal-Wallis and Mann-Whitney tests were used to detect differences between groups. A p value of <0.05 was considered significant. Statistics and graphs were generated using GraphPad Prism software.

**Results:** The median age of lupus onset for subjects with AG or AA at rs1876453 was significantly higher than subjects with GG [median (interquartile range[IQR]) 40 (21) for AA (n=31), 32 (17) for AG (n=488), and 30 (19) for GG (n=5175),  $p < 0.0001$ ]. When stratified based on sex, both females and males with the protective allele had significantly delayed disease onset [median (IQR) 40 (21.75) for AA (n=30), 32 (17) for AG (n=439), and 30 (18) for GG (n=4775) for females,  $p = 0.0006$ ; median (IQR) 37.5 (21) for AA + AG (n=50) and 30 (23.75) for GG (n=400) for males,  $p = 0.0083$ ].

**Conclusion:** The minor allele at rs1876453 delays lupus onset by 2-10 years. These data provide further support for a protective role for this SNP in lupus pathogenesis and suggest that novel therapies designed to mimic its mechanisms may prevent disease development in at-risk individuals.