

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

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BACKGROUND

- rs1876453 in *CR2* is associated with decreased susceptibility to lupus ($p^{\text{meta}}=4.2 \times 10^{-4}$, OR 0.85) (Zhao et al, Ann Rheum Dis 75:242, 2016)
- This association was particularly striking when subjects with lupus were stratified based on the presence of anti-dsDNA autoantibodies ($p^{\text{meta}}=7.6 \times 10^{-7}$, OR 0.71) (Zhao et al, Ann Rheum Dis 75:242, 2016)
- Anti-dsDNA antibodies are detected in patients with lupus a mean of 1.2 years before their initial symptom and a mean of 2.2 years before their diagnosis (Arbuckle et al, N Engl J Med 349:1526, 2003)

HYPOTHESIS

- Lupus patients with the minor protective allele at rs1876453 will have delayed onset of lupus compared to patients with the major allele

METHODS

- DNA from 5382 patients with SLE recruited from multiple sites was genotyped for rs1876453 on the Oklahoma Medical Research Foundation (OMRF) Illumina iSelect platform as part of the Large Lupus Association Study 2 (LLAS2)
- Global ancestry was estimated based on the genotype of ancestry informative markers
- Age of onset was collected by chart review
- 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.
- Institutional review board approval was obtained for LLAS2 at OMRF and at each of the contributing sites.

PARTICIPANT CHARACTERISTICS

LLAS2 Demographics				
Characteristics	GG n=4703	AG n=648	AA n=36	p value
Females, n (%)	4320 (92)	586 (90)	35 (97)	0.227
European American, n (%)	2643 (56)	370 (57)	30 (83)	0.0045
African American, n (%)	1164 (25)	204 (31)	6 (17)	0.0005
Hispanic, n (%)	896 (19)	74 (11)	0	<0.0001

n, number in sample

RESULTS

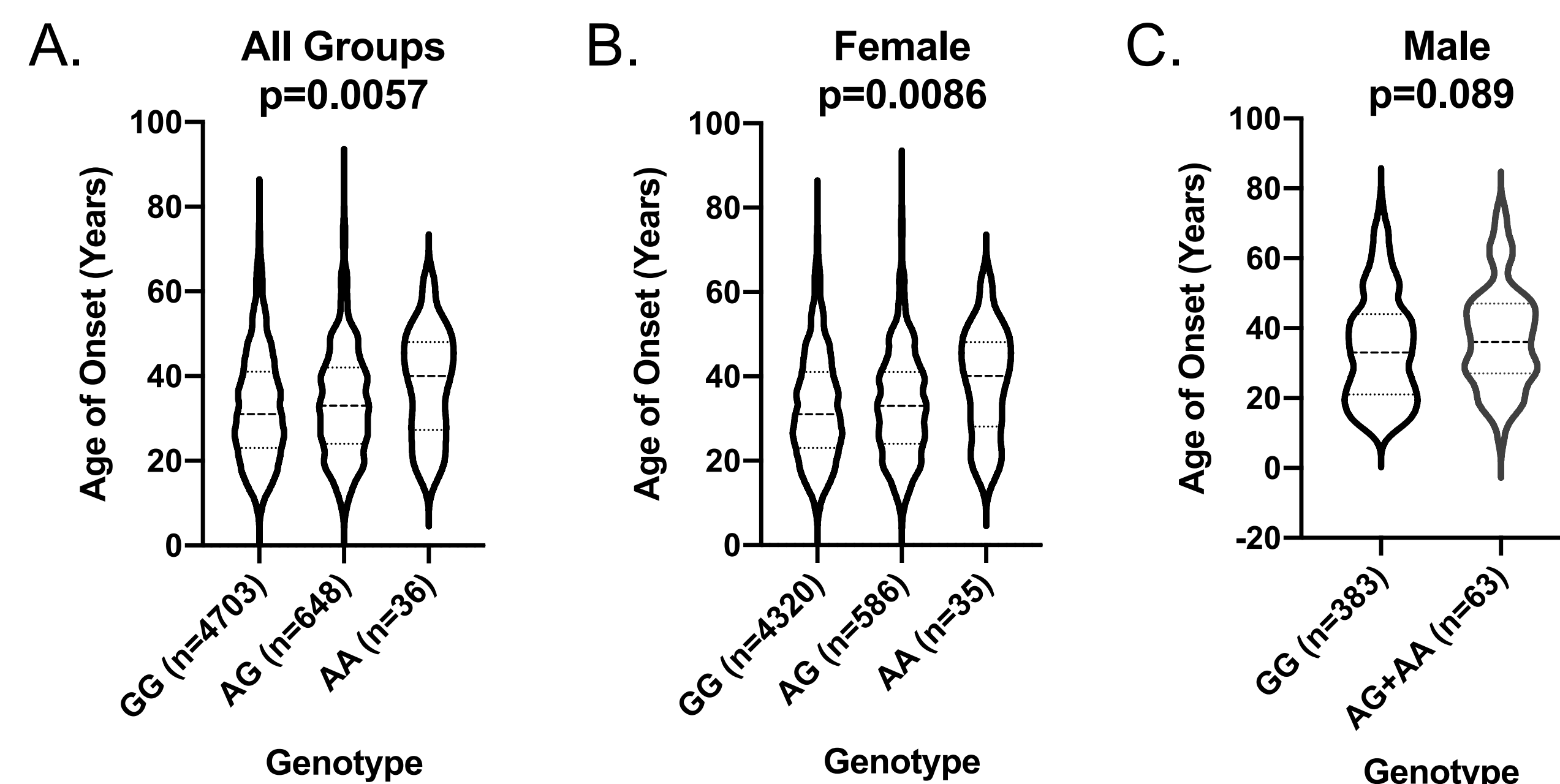


Figure 1. Lupus onset is delayed in subjects with the minor allele at rs1876453. The median age of lupus onset for subjects with AG or AA at rs1876453 was significantly higher than subjects with GG at the SNP [median (IQR) 40 (27.25-48) for AA, 33 (24-42) for AG, and 31 (23-41) for GG] (A). When stratified based on sex, females with the protective allele had significantly delayed disease onset (B) [median (IQR) 40 (28-48) for AA and 33 (24-41) for AG versus 31 (23-31) for GG], and males showed a similar difference (C) [median (IQR) 36 (27-47) for AG+AA versus 33 (21-44) for GG], though this was not statistically significant because the male cohort only had 40% power to detect a difference of 3.09 between the means with a significance level of 0.05 (two tailed).

CONCLUSIONS

- The minor protective allele at rs1876453 delays onset of lupus
- Subjects with one copy of the protective allele develop lupus a median of 2 years later than subjects without the protective allele
- Subjects with two copies of the protective allele develop lupus a median of 9 years later than subjects without the protective allele
- These data confirm the relevance of this polymorphism in lupus pathogenesis

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