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

Ani Oganesyan[1], Jennifer A Kelly[2], Stuart B Glenn[2], Adam J Adler[2], Adrienne H Williams[3], Mary Comeau[3], Julie T Ziegler[3], Miranda Marion[3], Marta E Alarcón-Riquelme[4,5], Graciela S Alarcón[6], Juan-Manuel Anaya[7], Sang-Cheol Bae[8], Dam Kim[8], Hye-Soon Lee[8], Lindsey A Criswell[9], Barry I Freedman[10], Gary S Gilkeson[11], Joel M Guthridge[2], Chaim O Jacob[12], Judith A James[2,13,14], Diane L Kamen[11], Joan T Merrill[15], Kathy Moser Sivils[2,13], Timothy B Niewold[16], Michelle A Petri[17], Rosalind Ramsey-Goldman[18], John D Reveille[19], R Hal Scofield[2,14,20], Anne M Stevens[21], Luis M Vilá[22], Timothy J Vyse[23], Kenneth M Kaufman[24,25], John B Harley[24], Carl D Langefeld[3], Patrick M Gaffney[2], Elizabeth E Brown[26], Jeffrey C Edberg[6], Robert P Kimberly[6], Betty P Tsao[11], Daniela Ulgiati[27], Kenneth L. Jones[28], Susan A Boackle[1,29]

[1]Division of Rheumatology, University of Colorado School of Medicine, Aurora, Colorado, USA; [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA; [3]Department of Biostatistical Sciences and Center for Public Health Genomics, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [4]Medical Genomics, GENYO. Centre for Genomics and Oncological Research: Pfizer/University of Granada/Andalusian Regional Government, Granada, Spain; [5]Unit of Inflammatory Chronic Diseases, Institute of Environmental Medicine, Karolinska Institutet, Solna, Sweden; [6]Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA; [7]Center for Autoimmune Diseases Research (CREA), Universidad del Rosario, Bogotá, Colombia; [8]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, South Korea; [9]Rosalind Russell/Ephraim P. Engleman Rheumatology Research Center, University of California San Francisco, San Francisco, California, USA; [10]Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA; [11]Division of Rheumatology, Medical University of South Carolina, Charleston, South Carolina, USA; [12]Department of Medicine, University of Southern California, Los Angeles, California, USA; [13]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA; [14]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA; [15]Department of Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, USA; [16]Colton Center for Autoimmunity, NYU School of Medicine; [17]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [18]Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [19]Department of Rheumatology and Clinical Immunogenetics, University of Texas Health Science Center at Houston, Houston, Texas, USA; [20]US Department of Veterans Affairs Medical Center, Oklahoma City, Oklahoma, USA; [21]Janssen Pharmaceuticals, Spring House, Pennsylvania, USA; [22]Division of Rheumatology, Department of Medicine, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico; [23]Division of Genetics and Molecular Medicine and Immunology, King's College London, London, UK; [24]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [25]US Department of Veterans Affairs Medical Center, Cincinnati, Ohio, USA; [26]Department of Pathology, University of Alabama at Birmingham, Birmingham, Alabama, USA; [27]School of Pathology and Laboratory Medicine, Centre for Genetic Origins of Health and Disease, The University of Western Australia, Crawley, Western Australia, Australia; [28]Harold Hamm Diabetes Center, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; [29]Rocky Mountain Regional Veterans Affairs Medical Center, Aurora, Colorado, USA

BACKGROUND

- rs1876453 in *CR2* is associated with decreased susceptibility to lupus ($p^{meta}=4.2\times10^{-4}$, 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 ($p^{meta}=7.6\times10^{-7}$, 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)

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				

HYPOTHESIS

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

RESULTS

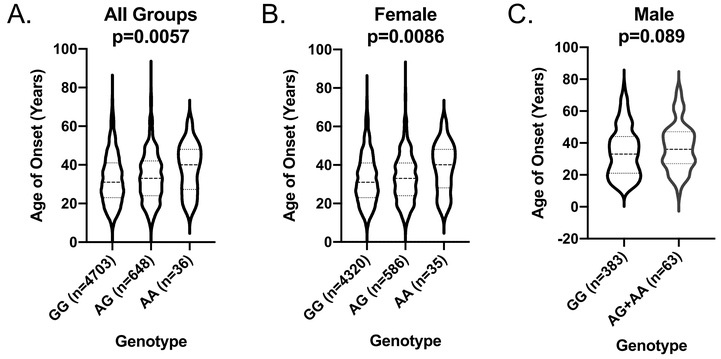

Figure 1. Lupus onset is delayed in subjects with the minor allele at rs1876453. The median age of lupus onset for subjects with AG or AA at rs1876453 was significantly higher than subjects with GG at the SNP [median (IQR) 40 (27.25-48) for AA, 33 (24-42) for AG, and 31 (23-41) for GG] (A). When stratified 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).

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.

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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