ABSTRACT NUMBER: 2341

The Interaction between Genetic Risk Factors and Age of Disease Onset in Juvenile Dermatomyositis

Claire Deakin[1], John Bowes[2], Lucy Marshall[1], Cerise Johnson[1], Gulnara Mamyrova[3], Rodolfo Curiel[4], Kelly A. Rouster-Stevens[5], Heinrike Schmeling[6], Adam Huber[7], Brian M. Feldman[8], Ann M Reed[9], Lauren M. Pachman[10], Soumya Raychaudhuri[11], Stephen Eyre[12] and Lucy R Wedderburn[1], [1]Infection, Immunity and Inflammation Programme, UCL Great Ormond Street Institute of Child Health, University College London, United Kingdom, London, United Kingdom, [2]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester, United Kingdom, [3]Rheumatology, George Washington University School of Medicine and Health Sciences, Washington, DC, [4]Department of Rheumatology, George Washington University, Washington, DC, [5]Pediatric Rheumatology, Emory Children's Center, Atlanta, GA, [6]Alberta Children's Hospital/University of Calgary, Calgary, AB, Canada, [7]IWK Health Centre, Halifax, NS, Canada, [8]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [9]Rheumatology, Duke University, Durham, NC, [10]Cure JM Program of Excellence in Juvenile Myositis Research, Stanley Manne Children's Research Institute, affiliated with Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [11]Division of Medicine and Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [12]Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom

Meeting: 2017 ACR/ARHP Annual Meeting

Date of first publication: September 18, 2017

Keywords: Aging, genetics, GWAS, juvenile dermatomyositis and juvenile myositis

SESSION INFORMATION

Date: Tuesday, November 7, 2017

Session Type: ACR Poster Session C

Session Title: Pediatric Rheumatology – Pathogenesis and Genetics Poster

Session Time: 9:00AM-11:00AM

Background/Purpose:

Juvenile dermatomyositis (JDM) is a rare, severe autoimmune disease characterized by muscle weakness and rash. Clinical features of JDM are heterogeneous, and can include serious complications such as calcinosis, ulceration, treatment-resistant rash and involvement of major organs, including gut, lungs and brain. While JDM and adult-onset dermatomyositis (DM) share similar clinical and biological features, there are differences in prevalence of clinical features. Cancer development is a major complication of DM, but not JDM. Conversely, calcinosis is a major cause of morbidity in JDM, but has a low occurrence in DM. The prevalence of myositis-specific autoantibodies (MSA), which are linked to different clinical features of disease, also differs between the adult and juvenile forms of the disease. These differences in the distribution of MSA and clinical features suggest an influential role for age of disease onset on the pathogenesis of disease.

Methods:

Caucasian JDM cases from the UK (n=312) were genotyped using the Illumina HumanCoreExome chip. Caucasian control data (n=2808) were obtained from the Wellcome Trust Case Control

Consortium. Following quality control, classical human leukocyte antigen (HLA) alleles and HLA amino acids were imputed using SNP2HLA. Logistic, linear and Cox regression were performed using PLINK and R package GenABEL, with adjustment for the first two principal components. Genome-wide significant association was set at $P < 5.0\times10^{-8}$ and suggestive association at $P < 1.0\times10^{-5}$. We subsequently built an international consortium to create a replication cohort of Caucasian cases from North America (n=475).

Results:

Case-control analyses confirmed involvement of HLA including multiple loci within *HLA-C* ($p = 1.35\times10^{-8}$, OR = 2.49, 95% CI = 1.82 – 3.42) and *HLA-DRB1* ($p = 2.73\times10^{-8}$, OR = 0.56, 95% CI = 0.46-0.69) at genome-wide levels of statistical significance. Outside the HLA region there was suggestive evidence of association at *ZNF337* ($p = 7.49\times10^{-6}$, OR = 1.81, 95% CI = 1.40-2.34), a zinc finger protein of unknown function. Analyses of association with age of disease onset did not implicate HLA involvement, suggesting the associations between HLA and JDM/DM are not influenced by age. Analysis of age of onset as a quantitative trait revealed suggestive associations at *PDE1A* ($p = 1.56\times10^{-6}$, $\beta = -1.61$, 95% CI = -2.26- -0.97) and *AGPAT3* ($p = 2.26\times10^{-6}$, $\beta = 1.63$, 95% CI = 0.97-2.30), genes involved in regulating intracellular cyclic nucleic acid concentrations and phospholipid biosynthesis/ Golgi-to-endoplasmic reticulum retrograde transport, respectively. In addition, we now have a replication cohort via our international consortium to validate these findings.

Conclusion:

This study has confirmed findings from previously published GWAS and Immunochip studies of JDM and DM concerning HLA involvement. Additionally, analyses of associations with age of JDM onset identified novel loci, *PDE1A* and *AGPAT3*, which if validated could suggest novel processes involved in pathogenesis. These findings will be confirmed in an independent replication cohort. Together with these validation samples, this study will be the largest GWAS of JDM to date.

Disclosure: C. Deakin, None; **J. Bowes**, None; **L. Marshall**, None; **C. Johnson**, None; **G. Mamyrova**, Cure JM, 2; **R. Curiel**, Cure JM, 2,BMS, 2; **K. A. Rouster-Stevens**, None; **H. Schmeling**, None; **A. Huber**, None; **B. M. Feldman**, None; **A. M. Reed**, None; **L. M. Pachman**, None; **S. Raychaudhuri**, Pfizer Inc, 2,Roche Pharmaceuticals, 2; **S. Eyre**, None; **L. R. Wedderburn**, None.

To cite this abstract in AMA style:

Deakin C, Bowes J, Marshall L, Johnson C, Mamyrova G, Curiel R, Rouster-Stevens KA, Schmeling H, Huber A, Feldman BM, Reed AM, Pachman LM, Raychaudhuri S, Eyre S, Wedderburn LR. The Interaction between Genetic Risk Factors and Age of Disease Onset in Juvenile Dermatomyositis [abstract]. *Arthritis Rheumatol.* 2017; 69 (suppl 10). https://acrabstracts.org/abstract/the-interaction-between-genetic-risk-factors-and-age-of-disease-onset-in-juvenile-dermatomyositis/. Accessed October 3, 2018.
