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

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**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 \( P < 5.0 \times 10^{-8} \) and suggestive association at \( P < 1.0 \times 10^{-5} \). 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 \( HLA-C \) \( (p = 1.35 \times 10^{-8}, \text{OR} = 2.49, 95\% \text{ CI} = 1.82 - 3.42) \) and \( HLA-DRB1 \) \( (p = 2.73 \times 10^{-8}, \text{OR} = 0.56, 95\% \text{ CI} = 0.46-0.69) \) at genome-wide levels of statistical significance. Outside the HLA region there was suggestive evidence of association at \( ZNF337 \) \( (p = 7.49 \times 10^{-6}, \text{OR} = 1.81, 95\% \text{ CI} = 1.40-2.34) \), 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 \( PDE1A \) \( (p = 1.56 \times 10^{-6}, \beta = -1.61, 95\% \text{ CI} = -2.26- -0.97) \) and \( AGPAT3 \) \( (p = 2.26 \times 10^{-6}, \beta = 1.63, 95\% \text{ CI} = 0.97-2.30) \), 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.

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