Genome-Wide Association Study of Dermatomyositis Reveals Shared Genetic Risk Factors with Other Autoimmune Diseases

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With The Myositis Genetics Consortium (MYOGEN)

Disclosure

Frederick W. Miller, M.D., Ph.D.
has no conflicts of interest to disclose.

Idiopathic Inflammatory Myopathies

- A heterogeneous group of syndromes whose hallmarks are chronic muscle weakness and muscle inflammation of unknown cause
- Estimated annual incidence is 5-10/million in adults, 1-5/million in children, estimated prevalence ~50-100/million
- Dermatomyositis, polymyositis, and inclusion body myositis are the most common clinical phenotypes
- Pathogenesis likely involves chronic immune activation in genetically susceptible individuals following exposure to specific environmental triggers
- Therapy consists of immunosuppressives to decrease tissue inflammation and rehabilitation to strengthen damaged muscles

Approaches

- An international myositis genetics consortium (MYOGEN) was established to study the genetics of myositis
- Objectives of the first MYOGEN study were to identify new genetic risk or protective factors for DM and assess possible genetic overlaps with other autoimmune diseases
- We performed a genome-wide association study (GWAS) on subjects of European ancestry meeting probable or definite Bohan and Peter criteria for DM using Illumina platforms
- Subjects studied were 1178 DM cases (705 with adult DM and 473 with juvenile DM) who were compared to 4724 geographically- and race-matched controls

Approaches - continued

- SNPs with call rate of <95% were excluded followed by excluding individuals with > 10% missing rates in genotypes
- Ingenuity Systems Pathway Analyses were performed on the genes identified by GWAS
- We further assessed the DM GWAS data for 140 non-MHC SNPs previously associated with RA, SLE, Crohn’s, T1D or MS

Dermatomyositis (DM)

- Myositis with the pathognomonic Heliotrope rash or Gottron’s papules
- Adult-onset and juvenile-onset forms exist with similar clinical and pathologic presentations
- Major genetic risk factors identified are HLA alleles
- DM shares many clinical and immunologic features with more common autoimmune diseases
- Family studies suggest a ~ 8 fold increased risk of autoimmune diseases in first degree relatives suggesting shared genetic risk factors

Miller 2005 In: Arthritis and Allied Conditions - A Textbook of Rheumatology; Ginn et al. 1998 Arthritis Rheum;
Niewold et al. 2011 Pediatrics
**Populations Studied**

<table>
<thead>
<tr>
<th>Population</th>
<th>Sample Size</th>
<th>Women (%)</th>
<th>Sample Size</th>
<th>Women (%)</th>
<th>No. of Successfully genotyped SNPs</th>
<th>Covariates</th>
<th>Genomic inflation factor (λ)</th>
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</thead>
<tbody>
<tr>
<td>Czech/Hungarian</td>
<td>178</td>
<td>70.80%</td>
<td>23</td>
<td>78.3%</td>
<td>243530</td>
<td></td>
<td>1.01</td>
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<tr>
<td>Spanish</td>
<td>43</td>
<td>81.40%</td>
<td>4</td>
<td>50%</td>
<td>23871</td>
<td></td>
<td>1.009</td>
</tr>
<tr>
<td>Swedish/Dutch</td>
<td>46</td>
<td>68.80%</td>
<td>4</td>
<td>75%</td>
<td>243544</td>
<td></td>
<td>1.021</td>
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<tr>
<td>UK</td>
<td>149</td>
<td>65.60%</td>
<td>150</td>
<td>70.40%</td>
<td>2415</td>
<td></td>
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<tr>
<td>USA</td>
<td>287</td>
<td>76.00%</td>
<td>280</td>
<td>69.60%</td>
<td>237155</td>
<td></td>
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<tr>
<td>Meta-analysis</td>
<td>700</td>
<td>75.4%</td>
<td>479</td>
<td>70.2%</td>
<td>241032</td>
<td></td>
<td>1.063</td>
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<tr>
<td><strong>Total</strong></td>
<td>705</td>
<td>72.4%</td>
<td>473</td>
<td>70.2%</td>
<td>4724</td>
<td></td>
<td>1.043</td>
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**Associations of Published GWAS Loci for Autoimmune Diseases with DM (P ≤ 0.015)**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr / Position</th>
<th>SNP Marker in Dataset</th>
<th>SNP Marker not in Dataset</th>
<th>P</th>
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<tbody>
<tr>
<td>B lymphoid tyrosine kinase: BLK</td>
<td>8 / 11381382</td>
<td>rs2736340</td>
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<td>0.000005</td>
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<tr>
<td>Chemokine (C-C motif) ligand 21: CCL21</td>
<td>9 / 34727282</td>
<td>rs2492358</td>
<td>rs951005:1.0</td>
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<td>Protein tyrosine phosphatase non-receptor type 2: PTPN2</td>
<td>18 / 12799340</td>
<td>rs1493217</td>
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<tr>
<td>Signal transducer and activator of transcription 4: STAT4</td>
<td>2 / 191672876</td>
<td>rs7574865</td>
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<td>0.00037</td>
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<td>Interleukin-2 receptor alpha: IL2RA</td>
<td>10 / 614672</td>
<td>rs7072793</td>
<td>rs1067778:0.935</td>
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<td>Interferon regulatory factor 3: IFNα</td>
<td>11 / 11036895</td>
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<td>SH2B adapter protein 3: SH2B3</td>
<td>12 / 110492139</td>
<td>rs653178</td>
<td>rs1284504:1.0</td>
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<td>Interferon regulatory factor 5: IRF5</td>
<td>17 / 123041419</td>
<td>rs94146581</td>
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**Summary**

- The first GWAS in DM confirmed a strong signal in the MHC region as expected (minimum p=2.79 x 10^-29), but no non-MHC SNPs met GWAS significance in this 1178 patient sample
- Assessment of 140 SNPs associated with autoimmune diseases indicates that DM shares many genetic features with other autoimmune diseases and suggests the presence of additional novel risk loci that require further study and confirmation
  - B lymphoid tyrosine kinase: BLK
  - Chemokine (C-C motif) ligand 21: CCL21
  - Protein tyrosine phosphatase non-receptor type 2: PTPN2
  - Signal transducer and activator of transcription 4: STAT4
  - Interleukin-2 receptor alpha: IL2RA
  - ER-resident transmembrane protein: ORMDL3
  - SH2B adapter protein 3: SH2B3
  - Interferon regulatory factor 5: IRF5

- Ingenuity Pathway Analysis of SNPs Associated with DM (P < 0.01)
  - Cut-off threshold p value = 0.05; P values (blue bars) left vertical axis; the ratio of the number of genes from the data set that map to a given pathway divided by the total number of molecules that comprise the pathway (yellow line connecting red bars) is shown on the right vertical axis.

- QQ Plots Showing Published GWAS Loci for AID with DM (Left) that are not Seen in Lung Cancer (Right)
Summary – cont.

• Canonical pathways that seemed particularly important in DM were those relating to T1D signaling, antigen presentation, the OX40 (CD134) signaling pathway, allograft rejection signaling, cytotoxic T cell-mediated apoptosis of target cells and graft vs. host disease signaling.

• The identification of common autoimmune disease genetic predispositions that promote the development of DM may lead to novel therapies for this disorder.

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• UK JDM Research Group – Coord. Lucy Wedderburn

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