The Clinical and Autoantibody Phenotypes of Juvenile Myositis

Cure JM Foundation Meeting

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Baltimore, MD

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NIEHS Program of Clinical Research
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Juvenile Idiopathic Inflammatory Myopathies

• A heterogeneous group of autoimmune diseases that share chronic muscle weakness and muscle inflammation of unknown cause

• Estimated annual incidence is 1-5/million in children, Peak age at onset: 7.5 years for JDM, Females are preferentially affected (~3:1)

• Clinicopathologic and autoantibody phenotypes differ in risk factors, presentations and outcomes

• Pathogenesis likely involves chronic immune activation in genetically susceptible individuals following exposure to specific environmental triggers
Conventional Classification of Myositis

**Clinical Subgroups**
- Adult polymyositis (PM)
- Adult dermatomyositis (DM)
- Myositis in overlap (CTM)
- Juvenile dermatomyositis (JDM)
- Malignancy-associated myositis
- Inclusion Body Myositis (IBM)

**Autoantibody Subgroups**
- Myositis-specific (MSA)
  - Anti-Synthetases (Anti-Jo-1)
  - Anti-SRP
  - Anti-Mi-2
- Myositis-associated (MAA)
  - Anti-U-RNP (U1, U2, U5)
  - Anti-Ro
  - Anti-PM/Scl
- MSA and MAA negative
Clinical Phenotypes Differ in Frequency in Adult and Juvenile Myositis

- Dermatomyositis (DM)
- Polymyositis (PM)
- Myositis with other CTD
- Cancer-associated (CAM)
- Inclusion body (IBM)
- DM sine myositis
- Immune-mediated necrotizing myopathy
- Macrophagic
- Eosinophilic
- Granulomatous
- Focal / Nodular
- Orbital

Clinical Phenotypes Differ in Presentation and Prognosis in Adult IIM

**DM**
- Mild to mod weakness, ILD, Myalgias, Arthritis, Cuticular overgrowth, V/Shawl rashes
- 75-90% 5 yr survival

**PM**
- Mod to severe weakness, ILD, CHF, Ventricular dysfunction, Arrythmias
- 75-94% 5 yr survival

**Overlap Myositis**
- DM > PM; Arthritis, Raynaud’s, Low CK
- 90% 5 yr survival

Love, 1991, Medicine; Rider and Miller, 2011, JAMA
### Demographic, Laboratory, and Autoantibody Differences among JIIM Clinical Phenotypes

<table>
<thead>
<tr>
<th></th>
<th>JDM (n=354)</th>
<th>JPM (n=33)</th>
<th>JCTM (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age at Diagnosis (years)</strong></td>
<td>7.4 Youngest</td>
<td>Oldest</td>
<td>Older</td>
</tr>
<tr>
<td><strong>Median Delay to Diagnosis (months)</strong></td>
<td>4.0</td>
<td>Longest delay</td>
<td></td>
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<tr>
<td><strong>Median CK Level (units/liter)</strong></td>
<td>♠ Lowest</td>
<td>⭐ Highest</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>ANA positive (%)</strong></td>
<td>72</td>
<td>61</td>
<td>84 Most frequent</td>
</tr>
<tr>
<td><strong>ANA titer (median)</strong></td>
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<td>Highest titer</td>
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</tbody>
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- ♠ Sig RF
- ⭐ Sig RF + LR
Demographic Differences Among JIIM Clinical Phenotypes

Races

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<thead>
<tr>
<th></th>
<th>White</th>
<th>Black</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>JDM</td>
<td></td>
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<tr>
<td>JPM</td>
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<tr>
<td>JCTM</td>
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Illness Onset

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<thead>
<tr>
<th></th>
<th>Severe onset</th>
<th>Slow onset</th>
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<tbody>
<tr>
<td>JDM</td>
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<tr>
<td>JPM</td>
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<tr>
<td>JCTM</td>
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</tbody>
</table>

Shah, Medicine, In press
JIIM Clinical Phenotypes are Distinct

**JDM**
- Gottron’s, Heliotrope, Malar, Periungual Capillary Changes, Photosensitive rashes (Malar, LEE, V sign, Shawl sign), Calcinosis, Lowest CK,

**JPM**
- Severe onset, Weight Loss, Falling, Raynaud’s, Cardiac, Highest CK

**Overlap Myositis**
- JDM > JPM, Malar Rash, LEE, Arthritis, Raynaud’s, ILD, Sclerodactyly. Intermed CK
Disease Courses Among JIIM Clinical Phenotypes

Monocyclic
Polycyclic
Chronic

% of Patients

JDM  JPM  JCTM
Outcome Differences Among JIJM Clinical Phenotypes

% of Patients

- Ever Hospitalized
- Calcinosis
- Wheelchair use
- Mortality

JDM  JPM  JCTM  Sig RF + LR
Adult and Juvenile IIM Clinical Phenotypes Share Some Features, Have Some Differences

- **Adult DM/PM**
  - 3-4 fold higher mortality (11-23% adult vs. 2.4 – 6.3% juvenile)
  - 3 – 7 fold more frequent lung disease (37-40% adult vs. 5-15% juvenile)

- **Overlap Myositis:**
  - Similar mortality (7% adult vs.15% juvenile)
  - Similar frequency lung disease (26-27%)

- **Many similar features, but a few differences in signs/symptoms:**
  - Adult DM/PM: ↑ DOE, Carpal Tunnel, Mechanic’s Hands
  - Adult DM: ↑ Myalgia, Arthritis, Raynaud’s, Palpitations
  - JDM and JPM: ↑ Distal Weakness, Falling, Muscle Atrophy, Asymmetric Weakness
Similar Autoantibody Phenotypes are Seen in Adult and Juvenile Myositis

- **Myositis-specific (MSA)**
  - Anti-synthetases
  - Anti-SRP
  - Anti-Mi-2
  - Anti-p155 (TIF-1γ)
  - Anti-MJ (NXP-2)

- **Myositis-associated (MAA)**
  - Anti-U-RNP (U1, U2, U5)
  - Anti-Ro52
  - Anti-PM/Scl
  - Anti-Ku

- **MSA and MAA negative**

Love, 1991, Medicine; Rider and Miller, 2011, JAMA
MSAs Target Translational and Transcriptional Factors

PM: Translational Factors
- Aminoacyl-tRNA synthetases
- SRP

DM: Transcriptional Factors
- Mi-2
- Transcriptional Intermediary Factor (TIF)-1γ (p155)
- NXP-2 (MJ)

Gunawardena, 2009, Rheum
Distribution of Autoantibodies in JIIM Patients by Clinical Subgroups

**JDM (n=354)**
- MSA-/MAA-: 35%
- Anti-synthetase: 22%
- Anti-Mi-2: 3%
- Anti-p155: 3%
- Anti-MJ: 28%

**JPM (n=33)**
- MSA-/MAA-: 31%
- Anti-synthetase: 9%
- Anti-Mi-2: 18%
- Anti-MJ: 9%

**JCTM (n=49)**
- MSA-/MAA-: 15%
- Anti-synthetase: 22%
- Anti-Mi-2: 17%
- Anti-p155: 12%
- Anti-MJ: 2%

Shah, Medicine, In press
Autoantibody Phenotypes Differ in Presentation and Prognosis in Adult IIM

**Anti-aminoacyl-tRNA Synthetases**
- Interstitial lung disease, Arthritis, Fevers, Mechanic’s hands
- 75% 5-year survival

**Anti-Signal Recognition Particle**
- Acute, severe muscle weakness, Myalgias, Cardiac involvement
- 25% 5-year survival

**Anti-Mi-2: Chromodomain Helicase DNA Binding Protein 4**
- Classic dermatomyositis, V-sign & shawl rashes, Cuticular overgrowth
- 100% 5-year survival

**Anti-p155: TIF-1γ**
- DM, CTM (DM), CAM (DM), V-sign & shawl rashes, Less lung disease

Love, 1991, Medicine; Miller, 1993, JAMA
### Demographic, Laboratory, and Autoantibody Differences among JIIM Autoantibody Phenotypes

<table>
<thead>
<tr>
<th></th>
<th>Anti-Synthetase n=19</th>
<th>Anti-SRP n=6</th>
<th>Anti-Mi-2 n=11</th>
<th>Anti-p155 n=131</th>
<th>Anti-MJ n=86</th>
<th>MSA/MAA neg n=121</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age at Diagnosis (years)</strong></td>
<td>Oldest</td>
<td>Oldest</td>
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<tr>
<td><strong>Median Delay to Diagnosis (months)</strong></td>
<td>Shorter delay</td>
<td>Shorter delay</td>
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<td></td>
<td></td>
<td>Shorter delay</td>
</tr>
<tr>
<td><strong>Median CK Level (units/liter)</strong></td>
<td>Intermediate</td>
<td>Highest</td>
<td>Highest</td>
<td>Lowest</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td><strong>ANA positive</strong></td>
<td>Rarely pos</td>
<td>Never pos</td>
<td>Rarely pos</td>
<td>Freq pos</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANA titer (median)</strong></td>
<td></td>
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</tbody>
</table>

**Sig RF**  **Sig RF + LR**

*Rider, Submitted*
JIIM Autoantibody Phenotypes Differ in Presentation and Prognosis

**Anti-aminoacyl-tRNA Synthetases**
Mix of clinical subgroups, Older, Interstitial lung disease, Arthralgia, Mechanic’s hands, Raynaud’s, Sclerodactyly, Intermediate CK

**Anti-Signal Recognition Particle**
JPM, Black, Oldest, Distal Weakness. Falling episodes, Raynaud's, Cardiac, Highest CK

**Anti-Mi-2**
JDM, Hispanic, Gottron’s, Malar Rash and Heliotrope, High CK,
New DM Autoantibody Phenotypes Differ in Clinical Presentation

**Anti-p155 (TIF-1γ)**
- JDM, JCTM (DM); White;
- Mod to severe weakness, Photosensitivity, GPs, Malar, V- and shawl sign, Cuticular OG, Erythroderma, Lipodystrophy

**Anti-MJ (NXP-2)**
- JDM>JPM; White;
- Muscle cramps, Dysphonia, Calcinosis, Contractures, GI ulcer, GPs, Malar rash, Periungual cap changes; Intermediate CK

Adult and Juvenile IIM Autoantibody Phenotypes Share Some Features, Have Some Differences

- **Anti-Synthetase Patients**
  - More Frequent overlap myositis in children, PM in adults
  - ↑ Raynauds, DOE, Mechanic’s Hands, ILD, Palpitations and Carpal Tunnel in adults
  - ↑ Falling, Muscle Atrophy and Distal Weakness in children

- **Anti-SRP Patients**
  - Higher mortality in adults
  - ↑ Palpitations, Myalgias, Carpal tunnel in adults
  - ↑ Falling, Muscle Atrophy in children

- **Anti-Mi-2 Patients**
  - ↑ Cuticular Overgrowth, V-sign and Shawl-Sign Rash, Carpal tunnel in adults
  - ↑ Falling in children
Proposed New Classification of Myositis Adult and Juvenile Patients

**Clinical Subgroups**
- Dermatomyositis  
  - (DM/JDM)
- Polymyositis  
  - (PM/JPM)
- Overlap Myositis  
  - (CTM/JCTM)
- Malignancy-associated myositis
- Inclusion Body Myositis (IBM)

**Autoantibody Subgroups**
- Myositis-specific (MSA)  
  - Anti-Synthetases (including Anti-Jo-1)
  - Anti-SRP
  - Anti-Mi-2
  - Anti-p155
  - Anti-MJ
- Myositis-associated (MAA)
- MSA and MAA negative
Possible Mechanisms for the Development of Myositis Phenotypes
Human Leukocyte Antigens (HLA) Important in Immune Response to Environmental Agents

- HLA molecules bind proteins and present them to the immune system
- HLA genes determine how people respond to environmental agents, including infections, toxins and other antigens
- HLA genes have been associated with many autoimmune diseases
One Common HLA Gene is Seen in Many Forms of Myositis, but Other Forms Have Different Genes

Clinical Phenotypes
- All Myositis
- Polymyositis
- Dermatomyositis
- Juvenile DM

Risk Genotypes in Caucasians
- HLA 8.1 ancestral haplotype: A1, B8, Cw7, DRB1*0301, DQA1*0501
- HLA A*68
- HLA B*50
- HLA DRB1*0701
- HLA DRB1*15
- HLA DQA1*0104
- HLA DQA1*0301

Autoantibody Phenotypes
- Anti-synthetase
- Anti-SRP
- Anti-Mi-2
- Anti-PM/Scl
- Anti-p155

Other Pro-Inflammatory Variants are Risk and Severity Factors for JDM

<table>
<thead>
<tr>
<th>Allele</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>TNFα-308 A*</td>
<td>↑ TNFα levels</td>
</tr>
<tr>
<td>IL1β+3953 T</td>
<td>↑ IL-1 levels</td>
</tr>
<tr>
<td>IL-1α+4845 T</td>
<td></td>
</tr>
<tr>
<td>IL1α-889 C*</td>
<td></td>
</tr>
<tr>
<td>Gm 13</td>
<td>↑ IgG levels</td>
</tr>
<tr>
<td>Gm 3 23 5, 13</td>
<td>Alter Ab binding affinities</td>
</tr>
<tr>
<td>Gm 1,3,17 5,13,21</td>
<td></td>
</tr>
<tr>
<td>PTPN22 R620W</td>
<td>Alters T cell signaling, ↑ autoreactive T cells</td>
</tr>
</tbody>
</table>

* Associated with calcinosis
Risk or protective factors are shown in **bold-face** or *italics*, respectively. TNFα -238G, IL-1RN VNTR A1, IL-1α +4845T, IL-1β +3953CT are additional risk factors for JDM that have not been evaluated in Adult DM, and HLA A*68 is an additional risk factor for Adult DM that has not been evaluated in JDM.
The genome wide association approach
Myositis Genetics Consortium (MYOGEN)

- Led by Frederick Miller, in collaboration with Peter Gregersen, over two dozen centers in North America and Europe have access to genetic material from over 2500 myositis patients and large numbers of controls
  - Centers contributing JDM patients include Lauren Pachman (Chicago), Ann Reed (Mayo), Lucy Wedderburn (London), Katalin Danko (Hungary), Jiri Vencovsky (Prague) and Lisa Rider (Bethesda)
- A first genome-wide association study of 1100 adult and juvenile Caucasian DM patients has been completed, which included 464 JDM patients
- Goal is to discover genetic factors that will improve our understanding of the disease process and lead to novel treatments
Manhattan Plot of GWAS Associations Showing a Major MHC Signal in Both DM and JDM

Miller et al with MYOGEN, Arthritis Rheum 2011
Genes Associated with Other Autoimmune Diseases Are Also Risk Factors for DM/JDM

Miller et al with MYOGEN, Arthritis Rheum 2011
MYOGEN – Where Do We Go From Here?

- **HLA region**
  - To understand major signal and where coming from
  - Examine other disease associations
    - Calcinosis, AutoAbs
- **GWAS**
  - Need more samples to find GWAS associations
- **Functional studies**
  - Discover new pathways important to cause of disease and develop new therapies
Ultraviolet Radiation (UVR) May Play a Role in the Pathogenesis of Dermatomyositis

• Anecdotally, UVR is associated disease onset and flares in lupus and DM

• Global UVR intensity correlates with the proportion of DM and anti-Mi-2 autoantibodies
  – Confirmed in US - 7 regions
  – Associated in women, not men, especially not African-American

Differences in Seasonal Birth Patterns in JIIM Subgroups Suggest Early Exposures

Distribution of Birth Dates for Hispanic JIIM Patients ($n = 42$)

Distribution of Birth Dates for Hispanic Controls ($n = 280$)

Seasonal
Sept 30

Uniform
Nov 28

Rank-Based Comparison of the Two Distributions, $p = 0.002$

Distribution of Birth Dates for p-155 Ab + JIIM Patients ($n = 28$)

Distribution of Birth Dates for p-155 Ab – JIIM Patients ($n = 31$)

Feb 16
Uniform

Seasonal
July 5

Rank-Based Comparison of the Two Distributions, $p = 0.003$

Vegosen, 2007, Arthritis Rheum
Further Evaluation of Genetic and Environmental Factors In Ongoing Studies

FAMILIES WITH TWINS OR SIBLINGS DISCORDANT FOR SYSTEMIC RHEUMATIC DISORDERS

Overview of This NIH Study

The Environmental Autoimmunity Group of the National Institutes of Environmental Health Sciences is currently enrolling families - in which an adult or child meets criteria for Rheumatoid Arthritis/Polymyalgia Juvenile Rheumatoid Arthritis, Systemic Lupus Erythematosus, Systemic Sclerosis or Myositis — and in which a twin or sibling of the same gender, who is within 4 years of age, does not have any of these 4 illnesses or another autoimmune disease. Patients remain under the care of their personal physicians while participating in the study. Compensation is available. There is no charge for study-related evaluations and medical tests at the NIH.

The goal of the study is to understand the genetic and environmental factors that may result in systemic rheumatic diseases.

The study will perform evaluations to assess why one twin or sibling developed disease and why the other brother or sister did not.

Subjects must be diagnosed within 4 years and may enroll at the NIH Clinical Center in Bethesda, Maryland or their local doctor's office.

Medical records, questionnaires and blood and urine samples will be collected at enrollment.

For each subject, annual questionnaire follow-ups will be collected by mail from up to 4 years after enrollment.

The development of new autoimmune diseases during the study will be tracked.

For Further Information About the Study, Please Call:
Dr. Lisa Rider: (301) 451-6272 or Email: lridr@mail.nih.gov
Frederick Miller: (301) 451-6280 or 1-(866) 271-3207

THE GEORGE WASHINGTON UNIVERSITY MEDICAL CENTER
WASHINGTON DC

Factors for Disease Flare in Adult and Juvenile Dermatomyositis and Polymyositis

MYORISK
Identifying Risks For Myositis

Doctors at the National Institutes of Health are conducting pioneering research in understanding the environmental risk factors that may result in an autoimmune disease called myositis. The goal of this study is to determine if certain infectious or noninfectious agents are associated with myositis and the anti-synthetase autoantibody groups. The study consists of completing surveys, collecting a house dust sample, a single clinic visit, and a blood draw. There is no charge for evaluations and medical tests at the NIH. Compensation is provided for both participants and their referring physicians.

You May Qualify If:
1. You have been diagnosed with adult or juvenile polymyositis or dermatomyositis
2. You were diagnosed within the last year
3. You are a healthy friend or cousin of a patient with polymyositis or dermatomyositis

Both Children and Adults are Eligible.

Location of the Study:
You may be enrolled at the NIH Clinical Center in Bethesda, Maryland, or at the NCRR Clinical Research Unit, Research Triangle Park, NC or in your local doctor's office.

Call Today Toll-Free: 1-(800) 411-1222
TTY: 1-(866) 411-1010
Se habla español
http://www.niehs.nih.gov/research/clinical/index.cfm
Department of Health and Human Services
National Institutes of Health
National Institute of Environmental Health Sciences
Environmental Autoimmunity Group

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Summary

• Distinct clinical and myositis autoantibody subgroups exist in JM patients and possess unique characteristics including: demographics, clinical features, laboratory data and outcomes.

  – While there are many similarities between the adult and juvenile myositis clinical and autoantibody phenotypes, there are some differences.
    • Frequency distribution of clinical and autoantibody subgroups differs between adult and juvenile myositis.
    • They each have some distinct clinical features.
    • Some adult subgroups have higher mortality

• Genetic and environmental factors appear to be distinct for the clinical and autoantibody subgroups.
  – HLA region and other autoimmune disease genes have been identified
  – Environmental factors may include UV light and perinatal factors
Understanding genetic and environmental risk factors for myositis will help identify disease pathways, lead to new treatments, and enable future prevention.
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Clare Weinberg, Min Shi, NIEHS

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AutoCure - curing autoimmune diseases

CureJM

MYOSITIS SUPPORT GROUP
Childhood Myositis Heterogeneity Study Group Members

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